DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Manya S. Deehr
Chief Legal Officer, General Counsel
Eurand
790 Township Line Road
Suite 250
Yardley, PA 19067

APR 30 2009

Re: Docket No. FDA-2009-P-0059

Dear Ms. Deehr:

This letter responds to your citizen petition received on February 9, 2009. Your petition requests that the Food and Drug Administration (FDA or Agency) take certain actions with respect to Solvay Pharmaceutical's (Solvay's) new drug application (NDA) 20-725 for a porcine-derived pancreatic enzyme drug product (PEP) (the to-be marketed product or TbMP). Solvay currently markets an unapproved PEP (the currently marketed product or CMP). Specifically, you request that FDA take the following actions:

1. Require that Solvay market and sell the TbMP using (a) a trade name other than Creon and (b) distinct and different packaging and trade dress that clearly distinguish the TbMP from the CMP.

2. Prohibit Solvay from suggesting in its sales and marketing efforts that data and findings generated in studies of the CMP are directly applicable to the TbMP.

Eurand states that it is the holder of a pending NDA for a PEP and currently markets two PEPs. We have carefully considered the issues raised in your petition. For the reasons stated in this response, your petition is granted in part and denied in part.

I. BACKGROUND

A. PEPs

Pancreatic enzyme preparations of porcine or bovine origin have been available in the United States for the treatment of children and adults with exocrine pancreatic insufficiency (EPI) since before the enactment of the Federal Food, Drug, and Cosmetic Act (the Act) in 1938. PEPs are used for treating patients with EPI from causes such as cystic fibrosis (CF), chronic pancreatitis, and pancreatectomy. PEPs are critical for the treatment of this vulnerable population, and the unavailability of appropriate PEP products can create a life threatening situation for children with CF and other patients with EPI.

Patients with EPI have deficiencies of endogenous lipase, protease, and amylase that lead to, respectively, deficient absorption of fats, amino acids, and carbohydrates. These deficiencies cause signs and symptoms of maldigestion and malabsorption. In patients with CF, particularly children, malabsorption leads to malnutrition. Malnutrition can result in growth failure in children. For both children and adults with CF, having a normal weight for age, height for age, and weight for height have been linked to improved survival.[1]

One notable risk of PEPs is fibrosing colonopathy (a stricture process of the colon), which has been associated with prolonged high-dose PEP administration particularly in younger patients with CF.[2] The etiology and pathogenesis of fibrosing colonopathy are undetermined, but reported cases have decreased with implementation of dosing guidelines promulgated by the Cystic Fibrosis Foundation (CFF Dosing Guidelines). The CFF Dosing Guidelines recommend maximum lipase doses that should not be exceeded.[3,4] The value of the CFF Dosing Guidelines in decreasing the risk of fibrosing colonopathy has been recognized by the FDA.[5] The CFF Guidelines were developed with input from FDA and were based on evidence in the medical literature.[6]

B. Regulatory Background

The majority of PEPs have not undergone review under NDAs, but PEPs have been commercially available since before the enactment of the Act in 1938 and the Drug Efficacy Study Implementation (DESI) requirements of 1962.

In the *Federal Register* of November 8, 1985 (50 FR 46594), FDA published a notice of proposed rulemaking to establish a monograph for over-the-counter (OTC) drug products to treat EPI. FDA evaluated the safety and effectiveness of drug products to treat EPI and determined that an OTC monograph would not be appropriate to regulate these drug products. In the *Federal Register* of July 15, 1991 (56 FR 32282), FDA withdrew the proposed rule and proposed a regulation to declare that OTC drug products used to treat EPI are not generally recognized as

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[1] Stallings et al. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. Journal of the American Dietetic Association 2008; 108:832-839.

[2] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ. High-Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis. NEJM. 1997; 336(18):1283-1289.

[3] Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J. Pediatric Gastroenterology and Nutrition 2002; 35:246-259.

[4] Borowitz D, Grand RJ, et al. Use of Pancreatic Enzyme Supplements for Patients with Cystic Fibrosis in the Context of Fibrosing Colonopathy. J. Pediatrics November 1995; 681-684

[5] FDA's guidance for industry, *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs* (PEP Guidance) is available on our Web site at http://www.fda.gov/cder/guidance/index.htm.

[6] A recent evidence-based review recommends adherence to the CFF Dosing Guidelines in patients with CF. Stallings et al. (see footnote 1).

safe and effective and are misbranded. The final rule, which affected only OTC products, published on April 24, 1995 (60 FR 20162).

In a *Federal Register* notice published on April 28, 2004 (69 FR 23410), FDA announced that all EPI drug products are new drugs and described the conditions for continued marketing of these drug products. In particular, FDA announced that manufacturers who wish to continue to market EPI drug products must submit NDAs. Under the Act, new drugs are required to be the subject of approved NDAs or ANDAs. With the exception of one PEP approved in 1996 and no longer marketed, PEPs have been marketed without approved NDAs. FDA also stated that it determined that prescription EPI drug products are medically necessary and, accordingly, would exercise enforcement discretion to allow manufacturers 4 years to obtain approved applications.

In April 2006, FDA published the PEP Guidance to assist manufacturers of EPI drug products in preparing and submitting NDAs. Among other things, the PEP Guidance describes chemistry, manufacturing, and controls information that should be provided in NDAs or drug master files for PEPs regarding the drug substance and viral safety (PEP Guidance at 3).

In a *Federal Register* notice published on October 26, 2007 (72 FR 60860), FDA announced that it intends to continue to exercise enforcement discretion to ensure the continued availability of EPI drug products after April 28, 2008. FDA announced that it intends to exercise its enforcement discretion with respect to unapproved PEPs until April 28, 2010, if the manufacturers have investigational new drug applications on active status on or before April 28, 2008, and have submitted NDAs on or before April 28, 2009. FDA stated that it was granting the extension to ensure the availability of EPI drug products during the additional time needed by manufacturers to obtain marketing approval.

As a result of these efforts, NDAs for PEP drug products are currently under Agency review.

C. Solvay's NDA

On December 2, 2008, a meeting of the Antiviral Drugs Advisory Committee (ADAC) was held as announced in a *Federal Register* notice published on November 4, 2008 (73 FR 65607). This meeting was held to discuss the safety and efficacy of Solvay's TbMP. A portion of this meeting was held in closed session to permit discussion of trade secret and/or confidential information.

D. Section 505(q) of the Act

Your petition is subject to section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which amended section 505 of the Act (21 U.S.C. 355) by adding new subsection (q). Section 505(q) of the Act applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 180 days after the date on which the petition is submitted. The 180-day period is not to be extended for any reason.

II. DISCUSSION

You request that FDA require that Solvay market and sell the TbMP using a trade name other than Creon and use packaging and trade dress that clearly distinguish the TbMP from the CMP (Petition at 9).[7] You also request that FDA prohibit Solvay from suggesting in its sales and marketing efforts, that data and findings generated in studies of the CMP are directly applicable to the TbMP (Petition at 9). We discuss your requests in greater detail below.

A. Requests Regarding Trade Name and Trade Dress

You request that FDA require that Solvay market and sell its TbMP using (1) a trade name other than Creon and (2) distinct and different packaging and trade dress that clearly distinguish the TbMP from Solvay's CMP.[8] To support these requests, you cite the following concerns:

1. The concurrent availability of the TbMP and CMP (Petition at 10).

2. The differences between the TbMP and the CMP, including FDA's prior findings that the comparability of the TbMP and CMP has not been demonstrated.[9] You note that the TbMP has a different formulation than the CMP (Petition at 10-13):
   - The CMP formulation contains a potentially hazardous phthalate, dibutyl phthalate.
   - The two products use different sources of porcine pancrease for the API and different extraction processing.
   - The CMP includes mineral oil, which, you state, is known to interfere with the absorption of certain essential fat-soluble vitamins.

3. The TbMP has not been clinically tested in children younger than 12 years of age, which raises questions about the demonstration of safety and efficacy in patients younger than 12 (Petition at 13-15).

4. You state that the TbMP and CMP could have different stability, different dosing instructions, and different labeled strengths, which would likely require different labeling. You believe different labeling will create confusion and could have a negative impact on safe use (Petition at 18-22).

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[7] You state that you first learned that Solvay had requested to use the trade name Creon for the TbMP based on the November 4, 2008, FR notice.

[8] You first raised these issues in a citizen petition received by the FDA on February 9, 2009, approximately 5 weeks from the expected regulatory action date for NDA 20-725 of March 20, 2009. You state that the information relating to your citizen petition first became available to you for consideration at the ADAC meeting of December 2, 2008.

[9] Hausman ED, Clinical Background Materials: Creon (Pancrelipase Delayed Release) For the Treatment of Pancreatic Insufficiency, December 2, 2008, FDA ADAC meeting (hereafter referred to as the FDA ADAC Brief — Open).

We respond to each of your concerns below.

1. Concurrent Availability of the CMP and TbMP

You suggest that patients will be confused by having both the CMP and the TbMP products in their homes and that pharmacists will be confused by having both products on pharmacy shelves (Petition at 10). You anticipate that there will be an extended period when both the CMP and TbMP will be on the market. However, FDA has worked with Solvay to develop an aggressive transition plan to replace the CMP in inventories with the roll-out of the TbMP. This transition plan will take place over a period of 8 to 12 weeks following introduction of the TbMP. The CMP will be withdrawn from wholesalers' inventories 30 days after distribution of the TbMP to wholesalers. The short overlap period during which both products will be available from wholesalers is designed to allow time for physicians to transition patients to new prescriptions for the new product. Based on sales and wholesaler distribution data, Solvay believes the CMP will no longer remain on retail shelves within 4 to 8 weeks after removal from wholesaler inventories. The transition plan will also include educational measures to inform pharmacists and health care providers on why the CMP must be replaced by the TbMP. The educational measures, including Dear Health Care Professional and Dear Pharmacist letters, as well as sales representative training and field activity, will explain the different dosing instructions and different labeled dosage strengths, the requirement for distribution of a Medication Guide as part of a Risk Evaluation and Mitigation Strategy (REMS) for the drug, and the need for a new prescription for the TbMP for patients currently taking the CMP. Health care professionals will be informed that because the CMP and TbMP are not interchangeable, when patients taking the CMP run out of their CMP, they will need to obtain a new prescription for the TbMP. A request for a refill of the CMP cannot be addressed by the pharmacist merely substituting the TbMP. Considering the transition plan and educational measures developed for the TbMP, we do not agree that the time the two products will be on the market concurrently is of such length that the use of the same trade name could mislead caregivers, health care professionals, and patients in a manner that would threaten patient health and safety.

2. Differences Between the TbMP and CMP

a. Comparability

You note that the Agency has previously concluded that comparability of the TbMP and the CMP has not been established.[10] FDA agrees that the CMP and TbMP are not comparable. We do not agree, however, that this lack of demonstrated comparability, or the other differences between the CMP and TbMP discussed below, warrant a change in the trade name of the TbMP.

b. Active Pharmaceutical Ingredient (API)

[10] FDA ADAC Brief — Open at 7.

The API of both the CMP and the TbMP is pancrelipase, which is comprised of amylase, lipase, and protease, as specified in the *United States Pharmacopeia.*[11] However, the API raw material for the two substances is obtained from different sources and is subject to different manufacturing processes. We do not agree however that the differences in animal source and extraction processing of the API between the CMP and the TbMP warrant a change in the trade name of the TbMP.

You state that the change in animal source between the CMP and the TbMP makes the CMP and TbMP different products and not interchangeable (Petition at 12). FDA agrees that the raw material and manufacturing processes for the two products are different. FDA also agrees that the CMP and TbMP are not comparable and not interchangeable.[12]

Under the transition timetable proposed by Solvay, the CMP and TbMP will overlap for a short time period. This transition plan and the inclusion of a clear statement in the product labeling for the TbMP that PEPs are not interchangeable support our conclusion that patient and prescriber confusion regarding the two Creon products should be minimal.

A prior example of a change made in a product's manufacture that did not require a change of the previous trade name is Synthroid. An NDA for Synthroid was submitted in response to a August 14, 1997, *Federal Register* notice that declared a class of already marketed products — oral levothyroxine sodium drug products — unapproved new drugs and required submission of 505(b)(2) applications for these products (62 FR 43535). This requirement was prompted in large part by variations in the stability and potency of a given dosage strength from lot to lot for products from the same manufacturer and the lack of approved oral levothyroxine sodium drug products on the market. This scenario for the oral levothyroxine sodium products is analogous to the current marketing situation for PEPs. Synthroid had a long history of marketing with its trade name before filing the 505(b)(2) NDA, and the same trade name was retained after review and approval of the NDA.[13]

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[11] *USP31–NF26.* Pancrelipase Delayed-Release Capsules, page 2909 (online edition 1-March-2009).

[12] Our determination that the CMP and TbMP are not comparable and interchangeable is based on the data and information before the agency in its review of this NDA. This conclusion does not necessarily mean a sponsor would not be able to demonstrate that PEPs manufactured using different animal sources (from the same species) or different processes are comparable. We note that the PEP Guidance stated that FDA "expects to receive only NDAs, including section 505(b)(2) applications, and not abbreviated new drug applications (ANDAs) for these products. For a pancrelipase or pancreatin product to be approved as an ANDA under section 505(j), the proposed drug product must be shown to contain the same active ingredients as an approved reference listed drug (21 CFR 314.92(a)(1)). Because of the complexity of pancreatic extract products, it is unlikely that currently available physiochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same. Therefore, the Agency has concluded that pancreatic extract drug products currently are not likely to be appropriate for ANDAs" (PEP Guidance at 2).

[13] You cite the Agency's denial of a petition requesting a trade name change for Prilosec (omeprazole magnesium) OTC to prevent confusion with the prescription-only product Prilosec (omeprazole capsules) (Petition at 24). You state that requiring a new trade name for the TbMP would accord with our decision in that instance. As previously discussed, numerous precautions will be taken by the applicant to assure confusion does not occur, including an aggressive transition plan and educational measures. Overlap of the two products on the market will be limited, and a new prescription will be required for the TbMP.

c. Excipients

You state that there are numerous differences between the CMP and TbMP products that are potentially clinically significant. These differences include that the CMP formulation includes a potentially hazardous phthalate, and the CMP includes mineral oil (Petition at 11-12).

We acknowledge that there are differences in excipients between the CMP and the TbMP, including removal of dibutyl phthalate and mineral oil from the CMP; however, we do not agree that these differences warrant a change in the trade name.

- **Dibutyl phthalate**

Dibutyl phthalate is an excipient in the CMP that will not be in the TbMP because of potential safety concerns arising from long-term exposures. Dibutyl phthalate has been shown to be an endocrine disrupter in preclinical models and is a reproductive and developmental toxicant in animals. The lack of dibutyl phthalate in the TbMP therefore provides a theoretical safety advantage relative to the CMP.

- **Mineral oil**

Mineral oil is not used in the TbMP. The removal of mineral oil eliminates it as a potential impediment to fat-soluble vitamin absorption.[14] Patients who have underlying exocrine pancreatic insufficiency are unable to adequately digest and absorb fat, which has a negative impact on their ability to absorb fat-soluble vitamins. PEPs enhance fat absorption, which helps to overcome this decreased ability to absorb fat-soluble vitamins. However, publications in the medical literature have found that despite vitamin D supplementation, patients with cystic fibrosis still have evidence of vitamin D deficiency on blood testing.[15] The Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis states that even with PEP therapy, fat-soluble vitamin absorption is not normalized.[16]

You state that if a prescriber mistakenly believes that the CMP and TbMP are the same formulation because they have the same name, the prescriber might not appreciate the differences in the mineral oil content between the two products and could fail to make necessary adjustments in vitamin supplementation (Petition at 17). You suggest this could lead to either under- or over-supplementation of fat-soluble vitamins (Petition at 17). There is no clear evidence that the small amount of mineral oil present in the CMP has necessitated an increase in fat-soluble vitamin supplementation in patients that take the CMP. It is well known that patients

[14] FDA regulations at 21 CFR 201.302 state that certain drugs for administration by internal use are deemed misbranded if they contain mineral oil.

[15] Rovner AJ, Stallings VA, et al. Am J Clin Nutr 2007; 86:1694-1699.

[16] Borowitz D, Baker RD, and Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J. Pediatric Gastroenterology and Nutrition 2002; 35:246-259.

with pancreatic insufficiency have fat malabsorption, a condition that causes impairment of absorption of fat-soluble vitamins. Patients with exocrine pancreatic insufficiency, such as cystic fibrosis patients, are seen by their health care providers regularly. Laboratory monitoring of fat-soluble vitamins is part of usual and standard care of these patients. The Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis recommends annual testing for vitamins A, D, E and K.[17] Thus, any change in fat-soluble vitamin level would be detected, and the need for vitamin supplementation adjustment would be implemented appropriately in the course of usual and standard care.[18] In addition, it is recognized that even with PEP supplementation that is considered "adequate," absorption of fat-soluble vitamins can remain impaired.[19] This has been attributed to the role of bile acids in absorption of fat-soluble vitamins. Patients with cystic fibrosis and exocrine pancreatic insufficiency are at higher risk of having concomitant liver disease, which could impair bile acid transit to the gut. Patients with exocrine pancreatic insufficiency on the basis of biliary tree obstruction could also have concomitant obstruction of bile acid transit to the gut.

As stated above, the removal of mineral oil is unlikely to result in hypervitaminosis D because even with aggressive supplementation, patients with fat malabsorption tend to run low serum vitamin D levels.[20] Rovner et al. found that CF patients taking PEPs demonstrated less than half the vitamin D absorption of healthy controls. A recent report on the vitamin A status in cystic fibrosis patients indicates that their serum retinol levels are significantly elevated compared to the reference population from the NHANES database (U.S. National Health and Nutrition Examination Survey 1999-2002).[21] The authors postulate that this finding may be attributed to (1) the aggressive supplementation of vitamin A in the cystic fibrosis population and (2) the use of vitamin products that contain water-miscible formulations of vitamin A to circumvent the fat malabsorption problems intrinsic to this patient population.

Solvay will provide information in a Dear Health Care Provider letter about the removal of mineral oil from the TbMP and will explain that this change necessitates assessment of patients' fat-soluble vitamin levels and possible dose adjustment of fat-soluble vitamin supplementation in response to the assessment results. Providing this information in the Dear Health Care Provider letter will enhance the clarity of the transition from the CMP to TbMP. Patients with exocrine pancreatic insufficiency (such as cystic fibrosis patients) are seen by their health care providers regularly as a standard of care, and laboratory monitoring of fat-soluble vitamins is part of usual care of these patients. Thus, any change in fat-soluble vitamin levels would be detected and vitamin supplementation adjustment would be implemented appropriately in the course of usual

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[17] Ibid.

[18] Consensus Conferences: Concept in CF Care. Pediatric nutrition for patients with cystic fibrosis. Volume X, Section 1. March 28-29, 2001.

[19] Borowitz D, Baker RD, Stallings V. J Pediatr Gastroenterol Nutr 2002; 35(3):246-259.

[20] Rovner AJ, Stallings VA, et al. Am J Clin Nutr 2007; 86:1694-1699.

[21] Maqbool A, Graham-Marr RC, Stallings V, et al. Vitamin A intake and elevated serum retinol levels in children and young adults with cystic fibrosis. J. of Cystic Fibrosis 2008; 7:137-141.

and standard care, even without the information on mineral oil and fat-soluble vitamins that will be included in the Dear Health Care Provider letter.[22] Therefore, given the educational measures being taken to inform health care providers about the removal of mineral oil from the TbMP and for the other reasons cited above, we do not agree that the lack of mineral oil in the TbMP warrants a new trade name for the TbMP.

3. Lack of clinical testing in children under 12 years of age

You state that the TbMP has not been clinically tested in some pediatric subpopulations, namely patients under the age of 12 years, and that it is unclear how the two products could have the same safety and efficacy profiles in children under 12 (Petition at 2). You state that it is unclear how the CMP and TbMP could have the same labeling and indications for children under 12 years of age (Petition at 14). You raise similar concerns regarding the efficacy of the TbMP for children under 12 years of age (Petition at 14-15).

Labeling for the TbMP will clearly state that the short-term safety and efficacy of the TbMP were demonstrated in one study of the TbMP in patients with cystic fibrosis 12 years and older. In the TbMP labeling, the USE IN SPECIAL POPULATIONS section, *Pediatric Use* subsection will state:

> The safety and efficacy of *pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients* (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis *have been described in the medical literature and through clinical experience.*" (emphasis added)

FDA intends to approve the TbMP without restriction, for children of all ages, and with dosing guidelines (the CFF Guidelines) that have been publicly available for more than 10 years. A recent evidence-based medicine review has re-affirmed these guidelines.[23]

Taking into account (1) the evidence in the medical literature of safety and efficacy of PEPs for treatment of exocrine pancreatic insufficiency, (2) that the disease characteristics and pathophysiology are similar across age groups, and (3) that the site of action is local within the lumen of the gastrointestinal tract, children younger than 12 are expected to respond to treatment as do children 12 and older and adults. Therefore, the Agency has determined it is appropriate to extrapolate both efficacy and safety data for the TbMP from children 12 years of age and older to children younger than 12 years.[24] Solvay will be required under the Pediatric Research and

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[22] Consensus Conferences: Concept in CF Care. Pediatric nutrition for patients with cystic fibrosis. Volume X, Section 1. March 28-29, 2001.

[23] Stallings V, Stark LJ, Robinson KA, Feranchak AP, et al., Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. J Am Diet Assoc 2008; 108:832-839.

[24] See Section II.B.3., infra, for further discussion of labeling and indication of the TbMP for children younger than 12 years.

Equity Act to develop an age-appropriate formulation for children whose weight dictates a lower capsule strength than is currently available for the TbMP.

4. Confusion Caused by Different Labeling, Including Strength, Dosing Instructions and Stability

Among the differences between the CMP and TbMP that you state have the potential to mislead caregivers, health care professionals, and patients — and potentially compromise patient health — are that the two products will likely have different labeling, including different labeling claims with respect to lipase activity, changes to the labeling to show that the TbMP will have zero stability overage, and different dosing units and instructions (Petition at 18-22). You state that use of the same trade name and similar trade dress for these products has the potential to cause these individuals to believe that the familiar labeling for the CMP is also applicable to the TbMP (Petition at 18).

To support your claims, you state that the CMP and the TbMP will have different label claims in relation to lipase activity (Petition at 19). Specifically, you state that the label claims with respect to lipase activity for the CMP are 5,000, 10,000, and 20,000 units, whereas the lipase activity for the TbMP are proposed as 6,000, 12,000 and 24, 000 units (Petition at 19).

With regard to API content or strength, the CMP is labeled as containing 5,000, 10,000, and 20,000 lipase units. The TbMP will be labeled as containing 6,000, 12,000, and 24,000 units of lipase. The actual lipase ***activity*** is similar for the two products, and the difference in labeled lipase units in the TbMP labeling relative to the CMP reflects labeling changes that were made to meet FDA's requirement to label the actual amount of lipase in a capsule at production, including overage.[25] (The CMP contains a higher amount of lipase than labeled.) The TbMP labeling will more accurately reflect the lipase content of the product, which could minimize the risk of overdosing and, hence, the risk of fibrosing colonopathy.

As part of its transition plan, Solvay will issue letters to health care professionals and dispensing pharmacists. These letters will explain the new labeling regarding lipase units and state that this reflects greater accuracy in labeling regarding overfill. Overfill in PEPs has been discussed in the pancreatic exocrine insufficiency medical literature in the past decade, and many health care professionals who care for these patients already understand this manufacturing concept as it pertains to this product class.[26] The letters will also point out the difference in the DOSAGE AND ADMINISTRATION section of the product labeling of the CMP and the TbMP and explain how to transition dosing (one capsule of TbMP for one capsule of CMP).

As stated in the labeling, PEP dosing is guided by symptomatic response to treatment in conjunction with "not-to-exceed" doses outlined in the CFF Dosing Guidelines. The apparent difference in number of lipase units is relatively small and is unlikely to prompt a significant change in the recommended starting dose for the TbMP in patients switched from the CMP by a clinician who has not read the Dear Health Care Professional letter. If a health care professional

[25] PEP Guidance at 6.

[26] Yankaskas JR, Marshall BC, et al. Cystic Fibrosis Adult Care. Chest 2004; 125:1S-39S.

is confused, does not understand that the new lipase unit labeling reflects an accurate description of lipase units, AND does not read the DOSAGE AND ADMINISTRATION section of the labeling, the predicted error resulting from assumptions based on his or her understanding of the CMP will be under-dosing of the TbMP. If the lower dose is clinically relevant, it will manifest as gastrointestinal symptoms that normally prompt contact with a health care provider and assessment for the need for dose escalation. If the patient does not experience gastrointestinal manifestations of fat malabsorption, a negative impact of dose reduction is unlikely, and any subtle clinical changes will be detected on routine clinical follow-up of the patient.

Dosing instructions for the TbMP in the DOSAGE AND ADMINISTRATION section of the labeling is by lipase unit, in conformity with the CFF Dosing Guidelines. Consistent with the CFF Dosing Guidelines, the dosing instructions will state that the dosage "should be individualized based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet."

The indication for both the TbMP and the CMP includes patients with exocrine pancreatic insufficiency. The indication for the TbMP will be "the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions," whereas the indication for the CMP is "for patients with pancreatic exocrine insufficiency as is often associated with cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal bypass surgery (e.g., Billroth II gastroenterostomy), ductal obstruction from neoplasm (e.g., of the pancreas or common bile duct)." We do not anticipate any safety concerns arising from use of the same trade name and the language differences describing the indication for the TbMP; the intended populations remain the same.

Stability data for the TbMP has been submitted and considered by the Agency as recommended by the PEP Guidance and will be accurately addressed in the labeling for the TbMP, including an accurate expiration date for the TbMP.

In addition, because all PEPs share certain serious risks, such as fibrosing colonopathy, and because fibrosing colonopathy is related to lipase exposure, the Risk Evaluation and Mitigation Strategies (REMS) for the TbMP will include a Medication Guide that will supplement dissemination of information about the risks and benefits of treatment to patients. In the Medication Guide, only the TbMP will be mentioned.

Therefore, for the reasons discussed above, we do not agree that differences you mention — differences in the labeling between the CMP and the TbMP with respect to lipase activity, changes to the labeling to show that the TbMP will have zero stability overage, and different dosing units and instructions — require a different trade name for the TbMP.

B. Requests Regarding Sales and Marketing Information

You state that FDA should not permit Solvay to imply, in the TbMP's labeling or advertising, that the CMP data support the safety or effectiveness of the TbMP without, at a minimum, also noting that (1) the CMP is not comparable to or interchangeable with the TbMP and (2) FDA has found that the CMP data are only supportive of the TbMP safety and that they do not directly

substantiate the TbMP's safety or efficacy (Petition at 23). You state that such promotion would render the TbMP misbranded under sections 502(a) and 502(n) of the Act (Petition at 23). You also state that FDA should prohibit Solvay from suggesting in its sales and marketing efforts and promotional materials that (1) the TbMP has been evaluated in more than one completed study or (2) the TbMP is the subject of completed studies in children under 12 (Petition at 4).

We respond to these issues below.

1. Addressing the Interchangeability or Comparability of the TbMP and CMP in the TbMP Labeling and Advertising

The TbMP labeling will state that the TbMP is not interchangeable with any other pancrelipase product. The CMP is not otherwise mentioned in the TbMP labeling. The labeling will also contain a banner that states "new formulation" for the first 6 months of the TbMP roll out.

Educational measures, including a Dear Health Care Professional letter and a Dear Pharmacist letter, as well as sales representative training and field activity, will explain the need for a new prescription for the TbMP for patients currently taking the CMP. Health care professionals will be informed that because the CMP and TbMP are not interchangeable, when patients taking the CMP run out of their CMP, they will need to obtain a new prescription for the TbMP. A request for a refill of the CMP cannot be addressed by the pharmacist merely substituting the TbMP.

2. References to CMP Data in TbMP Labeling and Advertising

The labeling for the TbMP will clearly state that the TbMP has been evaluated in only one completed study of the short-term safety and efficacy of the TbMP. CMP study data are not cited in the TbMP labeling; however, studies evaluating the CMP are among studies published in the medical literature regarding the efficacy and safety of the class of PEPs. As stated in the PEP Guidance, the "Agency has determined that there is a considerable body of evidence that replacement of pancreatic enzyme has clinical benefit for patients with cystic fibrosis and chronic pancreatitis"[27] based on evidence in the medical literature. The PEP Guidance also states that a consequence of reduction in pancreatic function is "absorption of nutrients is impaired, with the resultant malnutrition and a host of secondary complications, including retarded growth and development, impaired immune response, infections, and bleeding

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[27] 2004 FR Notice (69 FR 23410) citing the November 19, 1978, report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. The articles referenced by the Advisory Review Panel are:

Graham DY. Enzyme Replacement Therapy of Exocrine Pancreatic Insufficiency in Man. NEJM 1997; 23:1314-1317.

Littman A and Handscom DH. Pancreatic extracts. NEJM 1969; 281:201-204.

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Jordan PH and Grossman MI. Effect of Dosage Schedule on the Efficacy of Substitution Therapy in Pancreatic Insufficiency. Gastroenterology 1959; 36:447-451,.

Marks IN and Bank S. Treatment of Steatorrhea Due to Pancreatic Insufficiency. Modern Treatment 1965; 2:326-334.

tendencies, among others" (PEP Guidance at 3-4). The PEP Guidance states that FDA expects to receive 505(b)(2) applications for these products and notes that "NDAs filed under section 505(b)(2) of the Act may include published articles along with a bibliography of clinical trials in lieu of clinical data" (PEP Guidance at 4). Accordingly, general references to evidence of safety and effectiveness of PEPs in the medical literature will be included in the TbMP labeling in several places, including labeling on fibrosing colonopathy, adverse reactions, postmarketing experience, and in the *Pediatric Use* subsection of the USE IN SPECIFIC POPULATIONS section of the labeling.

The DOSAGE AND ADMINISTRATION section of the labeling will state that the dosing recommendations are based on the CFF Dosing Guidelines, which were developed based on evidence from the medical literature.

3. Discussion of Safety and Efficacy in Children Younger Than 12 Years Old in TbMP Labeling and Advertising

The labeling will not state that the TbMP is the subject of completed studies in children under 12 years of age. However, in keeping with FDA's statements regarding the evidence of effectiveness of the PEP class of drugs for treatment of patients with exocrine pancreatic insufficiency in the PEP Guidance and the PEP Guidance's statement that published articles can be submitted in lieu of clinical data in NDAs filed under section 505(b)(2) of the Act, the labeling will include general statements regarding PEPs to reflect the evidence in the medical literature of the efficacy and safety of replacement of pancreatic enzymes in patients with exocrine pancreatic insufficiency. The USE IN SPECIAL POPULATIONS section, *Pediatric Use* subsection of the TbMP labeling will state:

> The safety and efficacy of *pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients* (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis *have been described in the medical literature and through clinical experience*. (emphasis added)

General statements regarding safety and efficacy of the PEPs for conditions that cause pancreatic insufficiency are supported by a series of reports in the medical literature, including review articles.[28]

On November 12, 2008, FDA's Pediatric Review Committee (PeRC) discussed the medical literature and the clinical data submitted in support of the NDA for the TbMP with regard to labeling of the TbMP. Given that the disease characteristics and pathophysiology are similar across age groups and the site of action is local within the lumen of the gastrointestinal tract, children younger than 12 years of age are expected to respond to treatment as do children 12 and older and adults. Therefore, the Agency has determined it is appropriate to extrapolate both efficacy and safety data for the TbMP from children 12 years of age and older to children

[28] See the enclosed list of reports and review articles in the medical literature.

younger than 12 years. The medical literature includes publications of studies of PEPs in adults and children. The endpoints of those studies include changes in the coefficient of fat absorption and stool frequency. These publications demonstrate that PEPs have efficacy, as measured by coefficient of fat absorption, in both adults and children. Based on the available evidence, the PeRC determined that safety and efficacy could be extrapolated from the TbMP clinical trial that included children older than 12 years of age to the younger pediatric age groups. The PeRC concurred that the TbMP indication would not need to be limited to the age group included in the studies conducted with the TbMP, i.e., the indication could be extended to all pediatric patients.[29] The PeRC met to review this decision on March 18, 2009, and the original decision was upheld.

The TbMP labeling will clearly identify that the source of the dosing recommendations found in its DOSAGE AND ADMINISTRATION section are based on published guidelines derived from evidence published in the medical literature.

Therefore, the product labeling of the TbMP will clearly delineate the studies that have been conducted with the TbMP as distinct from the studies conducted on other pancreatic enzyme products with different formulations of pancrelipase containing the same active ingredients (lipases, proteases, and amylases). The CMP product is not mentioned in the TbMP product labeling. Sales and advertising efforts by Solvay will need to conform to, and be consistent with, the approved product labeling.

III. CONCLUSION

As discussed in section II of this response, we have determined that (1) the TbMP may have a safety advantage relative to the CMP because of the removal of dibutyl phthalate, (2) the removal of mineral oil is intended to remove a potential impediment to fat-soluble vitamin absorption, and any change in fat-soluble vitamin levels would be detected and vitamin supplementation adjustment would be implemented appropriately in the course of usual and standard care, (3) the labeled dose more accurately reflects the lipase content of the product, which could minimize the risk of overdosing and the risk of fibrosing colonopathy, and (4) with improved chemistry, manufacturing, and controls standards, the TbMP is expected to have greater consistency in product quality. Therefore, we have concluded that there is no reason to preclude use of the same trade name Creon for the CMP and TbMP based on safety and/or efficacy considerations.

In addition, because the two products will have distinct labeling and trade dress and the TbMP product labeling will state that PEPs are not interchangeable, the Agency does not consider it

[29] The PeRC concurred with CDER's decision to waive studies in the youngest pediatric age group, newborns up to 1 month of age, because diagnosis of cystic fibrosis generally is not made until after 1 month of age. Even if an infant is part of a newborn screening program, test results and diagnostic work-up are often not complete until nearly 1 month of age. In addition, the small number of patients diagnosed in this age category and the geographic dispersal would make conduct of a study in this age group highly impracticable. Solvay will be required to develop an age-appropriate formulation for children whose weight dictates a smaller lipase unit dose than the lowest capsule strength currently available for the TbMP.

necessary to assign a trade name other than Creon to the TbMP. Also, we believe that the transition plan and educational efforts for the TbMP will alleviate any potential confusion caused by the use of the same trade name for the CMP and TbMP.

Sales and advertising efforts by Solvay will need to conform to the approved product labeling. FDA believes that the product labeling clearly distinguishes between the data derived from a clinical study of TbMP and clinical data from the medical literature regarding PEPs. Furthermore, the TbMP labeling will not state that (1) the TbMP has been evaluated in more than one completed study, (2) the TbMP is the subject of completed studies in children under the age of 12 years, or (3) the CMP is comparable to or interchangeable with the TbMP.

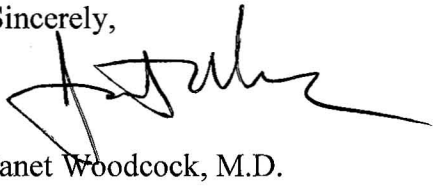
Improved labeling is not a cause for changing a product's trade name. FDA believes that any potential health care provider confusion caused by the improved labeling will be adequately addressed through the availability of the approved TbMP labeling, the dissemination of a Medication Guide, and Solvay's plan to educate health care providers and pharmacists regarding the labeling and how to transition patients from the CMP to the TbMP. Solvay's plan to remove the CMP from inventories over an 8- to 12-week period will minimize the time the two products will be available concurrently for sale. Solvay will remove the CMP from wholesaler inventories 30 days after distribution of TbMP to wholesalers. The short overlap time at the wholesaler level is designed to allow time for physicians to transition patients to new prescriptions for the new product. Based on sales and wholesaler distribution data, Solvay believes the CMP will no longer remain on retail shelves within 4 to 8 weeks after removal from wholesaler inventories. Any errors made by health care providers who do not read the TbMP product's DOSAGE AND ADMINISTRATION section of labeling or the Dear Health Care Provider letter will likely result in under-dosing, which, if clinically important, will manifest immediately as gastrointestinal symptoms — symptoms that are routinely managed by dose titration upward. Dose adjustment of PEPs based on gastrointestinal symptoms is part of routine management of the treatment population.

We do not find your argument that patients will be confused by having two different Creon products on their shelves at home compelling given the measures being taken to reduce any such confusion. Patients will be unlikely to replace their product supply with the TbMP until they are nearly out of their supply of the CMP. Patients will not be permitted to merely refill their CMP prescription with substitution of the TbMP. Pharmacists and health care providers will be educated that the two products are not interchangeable and that a new prescription for the TbMP is required when a patient needs to replenish their product supply. In addition, the distinctive packaging and trade dress of the two products will clearly distinguish between the products.

Therefore, for the reasons discussed above, your petition is granted in part and denied in part. Your request that we require Solvay to market the TbMP using a trade name other than Creon is

denied. As the TbMP will have distinct labeling and trade dress, your request that the products have trade dress that clearly distinguishes the TbMP from the CMP is effectively granted. Your request that we prohibit Solvay from suggesting in its sales and marketing efforts that data and findings generated in studies of the CMP are applicable to the TbMP is denied; however, Solvay's sales and marketing materials will need to conform to and be consistent with the TbMP's approved labeling.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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