

Background Information for Adventitious Agent Safety Control of Creon, a Pancreatic Enzyme Product Derived from Porcine Tissue

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Introduction

Pancreatic Enzyme Products (PEPs) are a mixture of digestive enzymes (lipases, proteases, amylases and other proteins) extracted from porcine pancreas glands, and used in the treatment of exocrine pancreatic insufficiency. Creon is the trade name of the PEP product that is closest to an approval action from the FDA. Typically, one production batch of Creon is manufactured from thousands of porcine pancreas glands, originating from swine of US, and European sources only. The glands are obtained from slaughterhouses certified by the USDA, and European authorities. Regulations for slaughterhouses focus on animal hygiene, review of veterinary records, herd surveillance and documentation of animal feeds.

Pig populations are known to transmit human pathogens such as influenza A and hepatitis E virus, and are known to harbor swine viruses that to date, have not been found to infect humans, but may have the potential to cross species barriers, such as porcine parvovirus or porcine circovirus 2. The vast majority of pigs coming to slaughter may only have been vaccinated to a limited spectrum of viruses, such as porcine circovirus 2 (principally in the USA), and typically will not have been vaccinated to porcine parvoviruses, which only appear to be pathogenic in pregnant sows. Thus, the possibility of contamination of the starting material with viruses relevant to both humans and swine is of great concern.

The ability of infectious disease agents to cross species barriers has been long recognized and new viral zoonotic diseases can appear which may pose a great danger to humans. Indeed, influenza viruses have both porcine and avian intermediary hosts in generation of influenza pandemics. It is thus possible that swine can be intermediate hosts for other infectious agents as well. Evidence that porcine parvoviruses, which are highly resistant to routine methods of inactivation, can infect humans is limited thus far to stable cultured human cell lines (Hallauer et al., 1971. *Archiv fur die gesamte Vursforschung* 35:80-90), while no evidence for their infectivity has been observed in pig farm workers (Wattanavijarn W. et. al., 1985 *Trans R Soc Trop Med Hyg* 79:561), or in hemophilia A patients treated with porcine factor VIII preparations. (Soucie, J,M, et, al., 2000. *Transfusion* 40: 708-711). Patients undergoing pancreatic islet transplants who are heavily immune suppressed, have been reported to have generated immune responses to porcine parvovirus, although cross reactivity to human parvoviruses appeared to account for such reactivity in some but not all of the patients. However, patients consuming PEP products, who consume such products several times daily for decades have never been evaluated for infection by porcine paroviruses delivered by the preferred infectious route. FDA (Dr. Jack Ragheb, Principle Investigator) is undertaking such a study, by investigating the presence of antibodies to porcine parvovirus in patients with cystic fibrosis.

The PEPs have been marketed in an unregulated fashion, since prior to 1938, and principally are used in Cystic Fibrosis (CF) patients and for other conditions associated with pancreatic exocrine insufficiency. These products are critical for preventing severe diarrhea in such patient populations. The vast majority of CF patients take PEPs for their entire lives. The impetus to bring PEPs into a

regulatory paradigm arose in response to cases of fibrosing colonopathy in the 1990s, which were felt potentially attributable to the PEPs, as in contrast to naturally released pancreatic enzymes, PEPs release further down in the small intestine and even into the colon where high local concentrations may damage colonic epithelium. FDA published a Federal Register notice in April, 2004, requiring New Drug Applications (NDAs) for these products, and published Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products in April, 2006 in order to elaborate FDA concerns in assuring the safety and efficacy of these products. The original deadline for NDA approval of all PEPs was April 28, 2008, which was changed to April 28, 2010 when it became clear that most manufacturers would not be able to meet the deadline.

In its guidance, FDA stipulated that all PEPs are considered non-interchangeable, that the 505(b)(2) route is the appropriate route for approval, and that to be approved, the NDA must meet requirements in 21 CFR 314.50 for human pharmacokinetic and bioavailability information and that efficacy must also be demonstrated and should include pediatric patients with CF.

As regards the issue of viral contamination of PEP products, the “Guidance For Industry: Exocrine Pancreatic Insufficiency Drug Products” stated the following:

- “A full viral risk assessment should be performed and justified by the Sponsor”
- “The manufacturing process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A” (Viral Safety Evaluation of Biotechnology Products derived from Cell lines of Human or Animal origin).

It should be noted that ICH Q5A sets a very high standard in demanding the best reasonable assurance that the product is *free of virus contamination* and requiring knowledge of how much virus may be present in starting material. It should also be noted that this document was intended for biotech products that are typically used for parenteral administration.

In fact, the viral safety issues have become more publicized in view of an article in the New York Times on April 1, 2008 (Seeking Alternatives to Animal Derived Drugs) specifically addressing pancreatic enzyme products and stating that the Cystic Fibrosis Foundation is working with the Altus Pharmaceutical Company to develop recombinant pancreatic enzymes. The article also alleges that FDA stated in 2006 that the viruses “must nonetheless be eliminated or rendered inactive”, which is not the case.

Viral Risk Assessment of PEPs

No quantitative viral risk assessments as described in ICH guidance Q9 “Quality Risk Management,” have been provided by Solvay Pharmaceuticals. However, informal risk assessments have been provided by Solvay Pharmaceuticals, and in addition to other sources including literature and discussions with experts, the following information is available regarding the risks encumbered by the presence of viral agents in these products.

Source Materials

- Swine origin: US/Europe sources only

- Pancreas glands derived from pigs raised and slaughtered for food. Vaccination of pigs for PCV2 and breeding sows for PPV is limited to some locations, primarily USA.
- Slaughterhouses are regulated under the auspices of the USDA and European Community (EC). Not regulated under CGMPs. Regulations for slaughterhouses focus on animal hygiene, review of veterinary records, herd surveillance and documentation of animal feeds. No other species are slaughtered and processed at the respective facilities.
- Glands are routinely frozen and transported to the production facility. No SOPs exist for organ harvest, (preventing contamination from other tissues), storage or transport of organs.
- Organ quality is monitored by visual inspection at the receiving facility by a licensed veterinarian. Frozen glands are quarantined for four-weeks pending notification of a disease outbreak.

Mitigation of Risk

FDA discussed the feasibility of sourcing animals from closed herds, or herds that had been vaccinated for PCV2 and PPV, and establishing SOPs for organ harvest, storage, transport. Solvay maintained the infeasibility of such approaches, given the number of glands needed to produce each lot.

Identification of viruses relevant to the safety and quality of Pancrelipase

B. Viruses Known to be Present in Swine

The pancreata are derived from pigs raised and slaughtered for food production purposes. Pig populations are known to transmit human pathogens such as influenza A and hepatitis E viruses, and are also known to harbor swine viruses that to date have not been found to infect humans, but which do have the potential to cross species barriers, such as porcine parvovirus. The vast majority of pigs for slaughter have not been vaccinated to viruses of concern. Pigs predominantly of US origin are vaccinated to porcine circovirus, and most breeding sows have been vaccinated for PPV, due to fetal wastage from this virus. Thus, contamination of the starting material with viruses relevant to both humans and swine is of great concern.

The ability of infectious disease agents to cross species barriers has long been recognized and new viral zoonotic diseases have appeared from time to time which may pose a great danger to humans. Indeed, influenza viruses have both porcine and avian intermediary hosts in generation of human influenza pandemics. It is thus possible that swine can be intermediate hosts for other infectious agents as well.

The porcine viruses can be divided into two broad categories, enveloped and non-enveloped.

Enveloped Viruses in Swine

- Enveloped viruses include African swine fever virus, transmissible gastroenteritis virus, eastern equine encephalomyelitis virus, classical swine fever virus, bovine viral diarrhea virus, porcine respiratory and reproductive syndrome virus, pseudorabiesvirus, paramyxovirus, swine influenza virus A, porcine endogenous retroviruses, suipoxivirus, rabies virus, porcine CMV, porcine lymphotropic herpesvirus, West Nile Virus, Hantavirus and Vesicular Stomatitis Virus.

Some of these enveloped viruses are transmissible from pigs to humans and can cause disease including the following:

- Influenza virus A (,airborne)
- Nipah Virus & Menagel Virus (paramyxoviruses)
- Vesicular Stomatitis Virus (aerosols),
- Pseudorabiesvirus (dsDNA, traumatic inoculation)
- Rabies virus (ssRNA, bite)
- West Nile virus(mosquito bite)
- Hantavirus (Rodent-borne)
- Eastern equine encephalomyelitis (mosquito bite)

Influenza virus A

There has been longstanding recognition of swine influenza virus as a zoonotic agent with serious public health risks. Although some studies have reported transient viremia (Brown et al., 1993. Vet Rec 132:598-602), in most cases the virus does not invade beyond the respiratory tract to any great extent and given that the route of transmission of this agent oronasal, the risk associated with the use of PEPs, absorbed enterally, should be reduced.

Paramyxoviruses represent a diverse group of viruses, some of which may present a public health risk. **Nipah Virus** is an RNA virus that has clearly been shown to infect humans causing encephalitis with high mortality and thus is a serious public health concern. Swine are thought to be a major source of transmission to humans. However, it is believed this virus has been eliminated from domestic swine. **Menagel Virus** is another porcine paramyxovirus detected in swine from Australia where human infections resulting in a sudden onset of fever, severe headaches and myalgia have been reported (Paul et al., 2003. Exogenous Porcine Viruses In: Xenotransplantation Eds. Salomon, D.R. and Wilson, C. Springer, NY). Information on the epidemiology on the Menagel virus is limited. Given the occurrence of these viruses in European and U.S. sourced swine, we believe that the risk associated from this associated with the use of Creon should be reduced.

Vesicular Stomatitis Virus

VSV is a virus in the family [Rhabdoviridae](#). The genome of the virus is a single molecule of negative-sense RNA. This virus can infect humans but is usually associated with mild influenza like conditions. However, there have been reports of childhood encephalitis associated with vesicular stomatitis virus infection (Quiroz et al, 1988. Am. J. Trop. Med. Hyg., 39, 1988, pp. 312-314) indicating that infection with vesicular stomatitis viruses may cause severe disease. We wish the committee to comment on the risk associated with this virus.

Eastern equine encephalomyelitis

Although eastern equine encephalomyelitis virus (EEEV) is capable of infecting a wide range of animals including mammals, generally people only become sick through the bite of an infected mosquito. Humans, horses and other mammals do not circulate enough viruses in their blood to infect additional mosquitoes. There have been some cases where EEEV has been contracted through lab exposure or from exposure of eyes, lungs or skin wounds to brain or spinal cord matter from infected animals (Wikipedia.org/Eastern equine encephalitis virus). We wish the committee to comment on the risk associated with this virus.

Rabies virus

Swine are extremely rarely infected with rabies (1-2 cases/year in USA), believed due to the restricted access of farmed animals to wild animal sources, and to the fact that rabies is reportedly easily detected and infected animals eliminated from the herd (Dr. Bruno Chomel's presentation "Swine Zoonose", California Department of Food and Agriculture Animal Health and Food Safety Services). We wish the committee to comment on the risk associated with this virus.

Pseudorabiesvirus

Pseudorabies (PRV) infects swine and other domesticated animals producing neurological clinical disease that is often fatal (kluge et al. 1992. The State-Federal-Industry PRV eradication program culminated with the declaration by the PRV Control Board at the 2004 United States Animal Health Association (USAHA) meeting that all States had achieved Stage V- PRV-Free status (Eric Bush, National Surveillance Unit, 2006 NASHSS Outlook Quarter One. Limited evidence of human infections have been reported. (Umene K. 1999. Mechanism and application of genetic recombination in Herpesviruses. Rev Med Virol 9: 171-589). The propensity of this group of viruses to recombination could potentially lead to a new virus causing a public health concern.

West Nile Virus

Similarly, because of the reasons elucidated above for rabies virus, swine raised for food are rarely infected by West Nile Virus (WNV) or Hantavirus. The general consensus is that the primary reservoirs of West Nile are birds, especially crows, jays, sparrows, and grackles. The role of mammals, including swine, in the epidemiology of West Nile virus has not been fully evaluated. The results from experimental infection of pigs with WNV showed that pigs did not develop a detectable viremia or seroconvert, suggesting that pigs are not susceptible to WNV and that pigs are unlikely to play a significant role as amplifying hosts of WNV (Diseases of Swine 9th Edition, by Barbara E. Straw, et al. 2006; Teehee ML, et al. Archives of Virology, 150 (6): 1249-56, 2005).

Non Enveloped Viruses in Swine

Non-enveloped viruses in swine include Porcine Parvovirus, Encephalomyocarditis Virus, Foot and Mouth Disease Virus, Swine Vesicular Disease Virus, Porcine Teschoviruses, Vesicular Exanthema Virus, Porcine Enteric Calicivirus, Porcine Rotavirus, Reovirus, Porcine Astrovirus-1, Porcine Adenovirus A and B, Porcine Circoviruses 1 and 2, Porcine Respiratory Coronavirus, and Swine Hepatitis E Virus.

Some of these viruses are transmissible from pigs to humans and can cause disease, including the following:

- Swine Hepatitis E virus **HEV**(33 nm, RNA, fecal-oral),
- Encephalomyocarditis virus **EMCV**(28 nm RNA, oral),
- Swine Vesicular Disease Virus **SVDV/PEV9** (oral),
- Foot and mouth diseases virus **FMDV**(28nm, RNA, airborne)
- **Reo/Rota** virus (oral),

HEV

HEV raises several public health concerns. HEV, the causative agent of hepatitis E, is a single positive-stranded RNA virus without an envelope that causes enterically transmitted non-A and non-B hepatitis. This disease should not be confused with hepatitis C, also called parenterally transmitted non-A and non-B hepatitis, which is a common cause of hepatitis in the U.S. HEV is classified in a group called hepatitis E-like viruses. HEV is transmitted primarily by the fecal-oral route, and contaminated drinking water is the most commonly documented route of transmission. It is not known to be transmitted through needles, blood or other body fluids or through sexual contact. Hepatitis E is an important public health disease in many developing countries. In these countries, two antigenic types of HEV, Asian and Mexican have been identified. A third type of human HEV has been isolated from HEV non-endemic countries, which shows only a limited similarity to Asian or Mexican types, but is similar to swine HEV. The existence of a population of individuals in industrialized countries who are positive for antibodies to HEV has led to the hypothesis that an animal reservoir(s) for human HEV may exist. In the US, two cases of acute hepatitis E (HEV US-1 and HEV US-2) have been reported, which were genetically distinct from other known strains of HEV, but were closely related to each other and to the USA strains of swine HEV (about 98% amino acid sequence identity). Moreover, several novel isolates of HEV have been identified from patients in Taiwan which were closely related to strains of swine HEV from pigs in Taiwan.

The above evidence indicates that swine HEV is a zoonotic agent and has potential for transmission of disease to humans. The potential for cross-species infection by HEV raises a public health concern, particularly for high risk groups such as swine handlers, pig farmers, and meat handlers. Feagins et al (*J Gen Virol* 88, 912-917, 2007) demonstrated that commercial pig livers sold in local grocery stores in the USA were contaminated by HEV and that the contaminating virus remains infectious. Among the 127 livers from local stores in Blacksburg, VA and Ames, IA that were tested, 14 were positive for HEV RNA (11% positive). Two of the three PCR-positive pig-liver homogenates transmitted infection, as evidenced by detection of fecal virus shedding from inoculated pigs. Yazaki et al reported (*J Gen Virol* 84, 2351-2357, 2003) that commercial livers sold in local stores in Japan were contaminated with HEV with 7 out of 363 packages having detectable HEV RNA (1.9% positive) with viral loads ranging from 2 to 7 logs /per gram of liver. The infectivity of these was not tested. Moreover, in Yazaki's report, among ten patients who contracted sporadic acute hepatitis E, nine of them had a history of consuming grilled or undercooked pig liver 2-8 weeks before the disease onset, thus raising a public-health concern for food-borne HEV infection. To date, there have not been reported outbreaks of HEV in the US, only sporadic cases. This virus is a known zoonotic agent and thus of considerable concern regarding PEP products.

Encephalomyocarditis Virus

EMCV, a non-enveloped virus belongs to the genus *cardiovirus* in the family *picornaviridae*. EMCV is a rodent virus that has an extremely wide host range. Infection of swine most probably occurs by the oral route. Transmission has been demonstrated experimentally among pigs kept in close contact, a usual farm condition in most countries. Fatal myocarditis due to EMCV infection has been observed in primates, elephants, carnivores and rodents (Gaskin, J.M, et al. *Encephalomyocarditis in Zoo Animals. Proceedings of the Ist International Conferences on zoological and avian Medicine* 1978; Wells, et al. *J. Zoo and Wild. Med* 20(3): 291-296, 1989; *Elephant Care International Fact Sheet* by Susan Mikota, DVM). Study of the prevalence of EMCV antibodies among selected human populations in various regions of the world revealed

antibody rates among children ranging from 1 to 33%, while adults varied from 3.2 to 50%. The pattern of age-specific rates observed in the study populations suggests that EMCV infection occurs primarily during childhood. The results of this study indicate that EMCV infection in man is fairly common but that most cases are probably asymptomatic and/or unrecognized. There are clinical and pathological reports of fatal encephalitis in young children with associated myocarditis wherein the authors suggested EMCV as the possible etiologic agent, but virus studies were not performed to identify the causal agent. We believe EMCV should be considered as a zoonotic agent and thus of great concern in treatment with PEP products.

Porcine Rotaviruses and Reovirus

Rota and Reo viruses belong to the Reoviridae family and are non-enveloped small round viruses (~ 75 nm dsRNA). Rotaviruses are resistance to organic solvent treatment but sensitive to heat treatment. Rotaviruses are the most significant cause of severe gastroenteritis in young children and in animals. There are 7 distinct groups (A-G). Group A rotavirus cause diarrhea in pigs. Transmission is via the fecal-oral route. There has been speculation on the role of animal rotaviruses in human infections. By analysis of genome segments, several human strains revealed a NSP4B gene group and an NSP5/6 gene of porcine origin. This finding suggest interspecies transmission of rotavirus stains and or gene exchange, and may indicate the occurrence of at least 3 separate rotavirus transmission events between pigs and humans, providing convincing evidence that evolution of human rotaviruses is highly intermingled with the evolution of animal rotaviruses. In humans, rotavirus causes diarrhea, mainly in infants. Reo viruses have not been known to be an important cause of any human disease although Reo virus infection occurs often in human in respiratory and intestinal tracts. Most cases are mild or subclinical, usually without disease symptoms. Rotaviruses and Reoviruses should be considered as zoonotic agents, and thus of great concern in treatment with PEP products, especially given that diarrhea in the patient populations using PEPs may be attributed to excess amounts of fat in the diet or failure of PEP lipase activity, rather than to an infection.

Swine Vesicular Disease Virus

SVDV belongs to the genus enterovirus within the Picornaviridae family comprised of a small non-enveloped (30 nm) single-strand RNA genome. The SVDV is resistant to low pH treatment but can be inactivated at 69 °C. The SVDV is antigenically closely related to the human enterovirus Coxsackievirus B5 and genetic studies of a number of SVDV stains and epidemiologic information strongly suggest that a human Coxsackie B5 was specifically introduced into and infected swine several decades ago. Viruses can be transmitted by fecal-oral and respiratory routes. Tissues from pigs killed during the viremic period contain up to 10 million infectious particles per gram. Moreover, infection can occur via skin or mucosal lesions with succeeding formation of a primary vesicle. In lab personnel handling SVDV, seroconversion was observed in some cases without any signs of disease. Although infection does not appear to result in clinical symptoms, SVDV should still be considered as a zoonotic agent and perhaps of a more limited concern to PEP products.

Foot and Mouth Disease Virus

FMDV is a species in the Aphthorirus genus of the picornaviridae family and contains a single stranded RNA genome and a non-enveloped capsid. The virus is reported to be acid-labile and may not spread to most humans via consumption of infected meat because normally stomach acid will completely inactivate FMDV. FMDV is one of the most highly contagious livestock diseases in

the world with potentially severe economic consequences. Morbidity of FMD approaches 100% but the fatality rate does not exceed 5%, except that higher fatality rates are observed in young piglets. There is no treatment for FMD. Vaccination may be used to control outbreaks. Although it may be transmitted to humans by contact or ingestion, symptomatic infection in humans is extremely rare and requires direct exposure virus (Q&A: The risks to humans BBC News, April 25, 2005). Infection with FMDV in humans causes a transient low-grade fever with vesicles on the lips, hands and occasionally on the feet, as well as in the mouth. Although, FMDV has been substantially eliminated from Europe following WWII, an outbreak in the United Kingdom that rapidly spread among farm animals and spread to several EU countries including France (by March 2001) indicates that Foot and mouth disease remains a constant threat to European farm animals. Europe has taken steps to prevent the entry of the FMD virus into their region so risk has been substantially reduced. North America, has been free of FMD for many years. Given the animal surveillance and occurrence in swine populations in Europe and US, we believe risk to product safety is reduced.

Emerging Viruses

There are examples of viruses (HEV, Porcine Respiratory and Reproductive Syndrome Virus, PCV2, Porcine Lymphotropic Herpesvirus and Porcine Respiratory Coronavirus) which appear to have emerged in pigs over recent years. Several other viruses are present in a wide range of animals as well as in humans, but so far have not been reported in pigs. However, it is theoretically possible that pigs may also be susceptible to infection by agents not documented to have caused porcine infection including the following:

- Spumaviruses (Retroviridae; ss-RNA, enveloped)
- Lymphocytic choriomeningitis virus (Arenaviridae, ss-RNA, enveloped)
- Borna disease virus (Bornaviridae, ss-RNA, enveloped)
- Polyomaviridae (papoviridae, ds-DNA, non-envelope)

As these organisms may mutate to adapt and cause infection in pigs, FDA contends that all robust animal disease surveillance plans should be designed to evaluate outbreaks of illness caused by novel forms of viruses and other adventitious agents that have adapted to swine and that the risk to products arising from swine so affected be prospectively evaluated as well as retroactively evaluated following an outbreak

Viruses abundant in swine that pose low risk for human infection but have a potential risk to cross species barriers

Porcine Parvovirus risk Considerations

- PPV is a member of the parvoviridae family. PPV is a very small (18-26 nm) non-enveloped capsid and is ubiquitous in swine populations around the world
- Parvoviruses are extremely resistant to physico-chemical treatment, withstand 100° C for 30 min. Moreover, for PEP manufacturability, viral clearance steps are not feasible
- It may not be feasible to revise the manufacturing process to achieve an acceptable level of inactivation/ clearance without compromising enzyme activity by such means

- It thus appears that it is possible to eliminate contaminated lots only by testing, but, depending on the specific manufacturer's processing procedures, few or many lots could fail
- Feline PV has crossed species barrier to infect dogs
- Porcine parvoviruses have been found to date to only infect human cell lines in vitro (Hallauer et al 1971. Archiv fur die gesamte Vursforschung 35:80-90),
- Pig farm workers (N=56) who had close daily contact with PPV infected pigs for one year were not positive for PPV antibodies (Wattanavijarn W et al. 1985 Trans R Soc Trop Med Hyg 79:561)
- Patients receiving porcine factor VIII concentrate, known to have porcine parvovirus by PCR (not tested for infectivity) were seronegative for antibodies to PPV (Soucie JM et al 2000. Transfusion 40: 708-711).
- Patients undergoing porcine islet xenotransplantation have tested positive for reactivity to PPV, although cross reactivity to human parvoviruses may confound the interpretation of the data
- No studies evaluating CF patients using PEPs for the presence of antibodies to PPV have been published.
- Unlikely that routine cooking or curing of swine products completely eliminates PPV, but the load of PPV in porcine muscle is not known (or not published). Thus, there may or may not be widespread exposure of human populations to PPV via food consumption.

Porcine Circovirus Risk Considerations

- PCV is a small non-enveloped negative-sense, single strand DNA virus (17 nm) and is ubiquitous in swine populations around the world
- There is an avirulent form, PCV-2 and a virulent form, PCV-1, which is associated with a debilitating disease referred to as post weaning multisystemic wasting syndrome and other swine diseases (Meehan et al., J Gen Virol (1998) 79:2171-9)
- Porcine Circoviruses are resistant to physico-chemical treatment and live virus would be expected to be present in drug product
- Oral nasal route is believed to be the route of infection
- PCV has been shown to infect human cell lines (Hattermann et. al., (2004) Xenotransplantation 11: 284-294) but mixed results have been reported for evidence of PCV2 infection in humans
- Antibodies to PCV were reported in 30% of samples from hospitalized patients with fever of unknown etiology (Tischer et al., 1995., Arch Virol (1995) 140: 1427-1439) but antibodies to PCV might not necessarily indicate active infection with PCV but rather infection with related viruses sharing antigenic epitopes with PCV
- Has been identified as a low but potential risk as a zoonotic agent () because it produces persistent infections, is vertically transmitted and some genetic variability has been demonstrated which raises issues regarding the ability to change tropism (Parrish et al., 2008. Micro & Mol Biol. Rev p 457-470)
- PPV has expanded tropism from cats to dogs
- Unlikely that routine cooking or curing of swine products completely eliminates PCV2, but the load of PCV2 in porcine muscle is not known (or not published). Thus, there may or may not be widespread exposure of human populations to PCV2 via food consumption.

Facilities

The sourcing and manufacturing facilities are dedicated to the processing of swine tissue. However, FDA does not believe procedures are not in place to prevent cross contamination between individual lots during manufacturing of the drug substance.

Manufacturing capacity for viral inactivation

The process has two distinct viral inactivation steps. There are no steps that are expected to possess any significant capacity to remove viruses. Solvay has also evaluated the capacity of their manufacturing process to inactivate relevant viruses or model viruses. Not surprisingly, these studies indicate that there is a wide variation in the ability of the manufacturing process to inactivate swine viruses but that enveloped viruses show in general, a low resistance to physico-chemical inactivation while non enveloped viruses show a medium to high resistance to these treatments.

Other viral inactivation or clearance steps have been evaluated but no additional viral inactivation method has been identified that can successfully demonstrate acceptable PPV inactivation without adversely impacting product potency (i.e., adversely impact enzyme activity) to unacceptable levels. However, FDA believes that irradiation with UV light should be evaluated as this process has been successfully applied to preparations of porcine trypsin.

FDA regulatory approaches for other products

Regulatory management of parvovirus risk in FDA products: human parvovirus B19

Currently, establishments for whole blood donations do not screen for parvovirus B19. Hence, B19 positive blood units are currently being used to transfuse recipients, including those with sickle cell anemia. The risk/benefit ratio was deemed favorable because the high rate of past and latent infections in blood donors would severely limit the blood supply

Reovirus in an upstream production process

Production processes that utilize mammalian cells to produce pharmaceutical products are evaluated at multiple levels to assure that final product is free of adventitious virus. In the past when an adventitious virus is detected in the bulk during routine batch testing, the bulk has been discarded regardless of the ability of the process to clear viruses, particularly if there is any indication that the virus has some pathogenic potential. For example, when Reovirus was detected in the bulk parenteral product (that was not deemed medically necessary) multiple batches were rejected and the production shut down, despite the ability of the process to clear the virus and the inability to detect this virus in the final product using relatively sensitive methods. Production was restarted only after the Agency received adequate assurance of product quality. This reflects the policy of not relying on a signal step to ensure product is safe and taking a rigorous approach to risk versus benefit decisions.

Risk Mitigation for PEP products

Control of Enveloped Viruses that have a potential to cause disease

The ability of a process to provide adequate viral clearance must also take into account the potential incoming viral loads. Limited studies using model *enveloped* viruses were conducted by Solvay Pharmaceuticals' to estimate the input viral load to determine the adequacy of the manufacturing process to inactivate enveloped viruses. This evaluation indicated the presence of some viral nucleic acid but also a robust clearance. Therefore, no routine monitoring of enveloped viruses has been proposed by the applicant. However, it is important to point out that measuring the levels of one virus provides no guarantee that other, more relevant viruses are not found in higher titers. Additionally, it is FDA's experience that past results do not predict future occurrence. This is particularly noteworthy given the changes in viral loads in swine populations over the last 20 years (Paul et al., 2003. Exogenous Procine Viruses In: Xentransplantation Eds. Salomon, D.R. and Wilson, C. Springer, NY). We would also point to the approaches to viral safety described in ICH Q5A which clearly indicates that multiple levels of viral control including routine lot by lot testing should be used for viral safety evaluations. Thus, viral testing of the starting material for the absence of undesirable viruses that may be infectious or pathogenic in humans, evaluating the capacity of the production process to clear infectious viruses and testing the product at appropriate steps of all production batches for absence of contamination infectious viruses have evolved to provide a comprehensive, robust control of potential viral contaminations in biotechnology products. Indeed, section V ICH Q5A provides for the rationale and action plan for viral clearance studies and *virus tests* on purified bulk for viruses that are human pathogens. In such cases, "purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question".

It is FDA's position that to provide a more rigorous assessment of risk *all viruses identified as a potential risk to transmit human disease* should be evaluated and routinely monitored in every production batch (i.e., included in the batch release testing). Thus, our strategy is to have a quantitative assay for the viral load by PCR that is performed for each indentified virus for every lot of material. If PCR is positive, an evaluation that the manufacturing process is capable of providing excess clearance given the starting viral load is performed according to defined SOPs or specifications. Assays for infectivity may be employed to determine the final disposition of the product according to specification (i.e., if infectious particles are found, the lot is discarded). FDA seeks the committee's advice as to whether this is sufficiently stringent. Should PCR evidence of a potential human pathogen, though no infectious material is found, be sufficient of itself to determine elimination of the lot, even if the process is capable of reducing viral load to a level for example, where less then one viral particle per a thousand doses would be expected?

Control of non enveloped viruses that have a potential to cause disease

Solvay Pharmaceuticals' investigations of nonenveloped virus loads focused on those non enveloped viruses that show a high resistance with respect to physico-chemical inactivation. As a result of this analysis batch release testing for potential human pathogenic viruses that show high

resistance to physico-chemical treatments and cause significant human disease has been established. Similar caveats as described above for enveloped viruses also apply to non enveloped viruses. Thus, it is FDA's position that to provide a more rigorous assessment of risk *all* viruses identified as a potential risk to transmit human disease should be evaluated and routinely monitored in every production batch (i.e., included in the batch release testing). FDA believes every lot should be monitored by PCR testing for detection of the selected viruses. If PCR is positive, an evaluation that the manufacturing process is capable of providing excess clearance given the starting load, is performed according to defined SOPs or specifications. Assays for infectivity may be employed to determine the final disposition of the product according to specification (i.e., if infectious particles are found, the lot is discarded). In practical terms, those viruses that test positive by PCR and are only poorly inactivated by the process would be tested by infectivity assays, if available. If positive by infectivity, the lot will be rejected. FDA seeks similar advice as described for enveloped viruses.

Control of viruses abundant in swine that pose low risk for human infection but with some potential risk to cross species barrier

Porcine parvovirus (PPV) and Porcine Circovirus (PCV-1&2)) have also been identified that are ubiquitous in swine populations around the world and while they are not thought to be infectious to humans may present a safety risk if infectious virus is present in the drug product since viruses can sometimes change tropism (Parrish et al., 2008. *Micro & Mol Biol. Rev* p 457-470). Factors that are important contributors to increase frequency in changing species specificity include exposure levels, genetic stability of the virus.

Solvay Pharmaceuticals' investigations into the presence of porcine parvovirus in pancrelipase employed a quantitative PCR method and demonstrated the presence of high levels of PPV specific genomes in all lots tested. No PCR based tests for the presence of PCV1 or 2 were conducted but it would be expected that most, if not all lots would test positive. Solvay Pharmaceuticals also conducted in vitro PPV infectivity tests and demonstrated that some batches of Creon contained low levels of live PPV but that there was no correlation between the level of PPV genomic equivalents and the level of infectious PPV. Given the sensitivity of the tests and other considerations, it is possible that all batches (but not all doses) contain some live PPV. This possibility is expected to be similar for all manufacturers of PEPs. Tests to evaluate the presence of live PCV 1 or 2 have not been performed. It should be noted that a specification stating that all lots with live PPV must be rejected may restrict the availability of the product. FDA has considered establishing specifications for levels of infectious PPV and PCV and seeks guidance from the committee on this issue.

Proposed Risk Mitigation Strategy: Long term

Transition to recombinant or synthetic sources of PEPs

Summary

Although one additional method should be evaluated for its potential for inactivating PPV (namely UV irradiation), it is becoming clear to FDA that it may not be feasible to have potent PEP products in which live porcine parvovirus is completely eliminated, as steps taken to inactivate

virus also inactivate enzyme activity. It also is clear to FDA that the PEP products are absolutely medically necessary at this point in time to the well being of numerous patients with pancreatic insufficiency of various origins. Given the potential risk to individual patient, patient caretaker, and to the general public health of zoonoses arising from porcine sources, FDA deemed guidance from a committee of virologic and clinical experts imperative prior to approving PEP products. FDA specifically seeks evaluation of the risk posed by viral contamination of PEPs from live porcine parvovirus and PCV1, 2 that may be present in final product, , seeks feedback on the level of viral control necessary for these products, seeks feedback regarding surveillance and monitoring for novel zoonotic events, seeks feedback regarding mechanisms to contain and control such an outbreak, and finally, seeks to engender a discussion of the type of information that should be communicated to end users. Although the product of interest today is manufactured by Creon, there are numerous other manufacturers of PEP products that have similar and perhaps greater concerns.

Questions for Open Panel Discussion

1. What are the risks of generation of a novel zoonotic infection through consumption of material containing live porcine parvoviruses or porcine circoviruses? What are the risks of generation of a novel zoonotic infection from agents not currently known to infect swine? Please consider risks to the individual patient, patient caregivers, and the public at large. What approach provides an appropriate mitigation of the risks, associated with transmission of swine viruses while continuing supply of product, or should stricter controls be established?
2. What information should be provided to physicians and patients in product labeling regarding the risk from viral contaminations?
3. Is there additional information FDA or Sponsors should obtain in order to better understand the risk associated with adventitious viral agents? For example, FDA is engaged in a study to screen CF patients on long term PEP therapy for antibodies to PPV or PCV2 to assess whether there have been limited porcine parvovirus infections to date. Are there additional studies that could be informative as to risk? Do food sources such as muscle and liver contain significant levels of porcine parvo and circo viruses and does routine cooking temperatures or curing processes eliminate live viruses from food sources?
4. What specific recommendations can the committee offer regarding routine surveillance and monitoring for zoonotic events in patients treated with PEPs?

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Antiviral Drugs Advisory Committee Meeting
2 December 2008**

CLINICAL BACKGROUND MATERIALS

Creon (Pancrelipase Delayed-Release)

For the Treatment of Pancreatic Exocrine Insufficiency

**Prepared by Ethan D. Hausman, M.D
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Division of Gastroenterology Products
November 3, 2008**

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1 Executive Summary

1.1 Statement of Purpose

The purpose of the Advisory Committee meeting is to obtain advice from the Committee regarding the efficacy, safety, indication, and use of Creon (Pancrelipase Delayed-Release Capsules) in the context of the theoretical risks of viral transmission from the product to treated patients. The Applicant, Solvay Pharmaceuticals Incorporated, proposes the following indication:

“Treatment of maldigestion in patients with exocrine pancreatic insufficiency”

The Applicant proposes individualized dosing according to the “degree of steatorrhea present and the fat content of the diet” with therapy to be initiated at the lowest possible dose and gradually increased until the “desired control of steatorrhea” is obtained.

1.2 Background Summary

1.2.1 Regulatory History of PEPs

Pancreatic enzyme products (PEPs) are used to treat pancreatic enzyme insufficiency (PEI) and have been commercially available in the US and throughout the world as nutritional supplements and over-the-counter therapies since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938 and the Drug Efficacy Study Implementation requirements (DESI) of 1962. The majority of PEPs have not undergone evaluation and study under New Drug Applications (NDAs). The only product to receive FDA marketing approval is Cotazym® (sponsored by Organon, Inc), which is not currently marketed in the US. Therefore, no PEP is currently available to the US market under an approved NDA, and the only available products are marketed as non-prescription nutritional supplements.

In the 1990s FDA evaluated the safety and effectiveness of the PEPs in an effort to determine the appropriateness of allowing these products to be marketed as over-the-counter drugs. FDA determined that PEPs were firmly established in the clinical armamentarium for a number of primary diseases characterized by PEI such as cystic fibrosis (CF), and that a body of literature supported improved long-term outcomes and described the general safety profile of PEPs as a drug-class. This position is supported by a recent evidence-based review sponsored by the Cystic Fibrosis Foundation (CFF) that determined there was adequate evidence from population based studies showing that PEPs are associated with improved nutrition and that improved nutrition is associated with improved growth indices such as weight-for-height percentiles and that these improvements are associated with improved pulmonary function and survival in adults and children.¹ Therefore, FDA accepts that there is adequate evidence to support safety and efficacy of PEPs as a drug-class. However, FDA has determined the following issues could have clinically meaningful effects on safety and efficacy:

¹ Stallings VA, 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.

- Variation in bioavailability among similar dosage forms between manufacturers that could affect safety and efficacy.
- Variation in bioavailability within the same product from one manufacturer (e.g., lot-to-lot and within-lot variability) that could affect safety and efficacy.
- Since PEPs are porcine (pig-) derived products, potentially transmissible porcine viruses could affect safety.

Therefore, FDA determined that manufacturers had to demonstrate adequate safety, purity, potency, and manufacturing processes for each PEP. FDA determined that these requirements would be most appropriately assured by requiring that each PEP to undergo a product development process adequate to support FDA review and approval as a new drug. FDA also determined that the spectrum of diseases for which PEPs are used, such as CF, requires chronic medical monitoring and necessitates prescription only status.

Additionally, FDA noted that to comply with the Pediatric Research Equity Act of 2003 (PREA) (21 U.S.C. 355c), applications must contain data that are adequate to assess the safety and effectiveness for the claimed indications in each of the appropriate pediatric subgroups (newborns, infants, children and adolescents). FDA noted, however, that clinical studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.

FDA announced these decisions in the Federal Register on 28-April-2004 (71 FR 19524), and published a guidance document in the Federal Register of 14-April- 2006, (e.g., the PEP Guidance), intended to provide regulatory assistance to manufacturers that plan to submit NDAs for PEP therapies.² FDA intends to practice regulatory discretion (for example, FDA will not withdraw a PEP from the market) until 28 April 2010 for products under active IND on or before 28 April 2008 and under NDA on or before 28 April 2009.³ After that time, PEPs not meeting these deadlines will be subject to regulatory enforcement including removal from US distribution. In summary, enforcement discretion is product specific and requires due diligence toward an active marketing development plan.

As noted above, FDA recognizes that the weight of clinical evidence supports safety and efficacy of PEPs as a drug-class. FDA also recognizes that PEPs are useful for treatment of PEI due to a variety of primary processes including CF, chronic pancreatitis (CP), and pancreatectomy (e.g., surgical removal of the pancreas). Therefore, FDA has determined that a PEP drug development program can rely on a single adequate and well-controlled study to demonstrate safety and efficacy in the context of new drug development and NDA review.² The PEP Guidance states that sufficient clinical evidence of safety and efficacy from a study of 10 to 25 patients with CF could provide adequate clinical data to support a new drug marketing application for a candidate PEP.

² U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). “Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs” April 2006; <http://www.fda.gov/CDER/guidance/6275fn1.htm>.

³ Federal Register (FR) Notice: 71 FR 19524, 14-April-2006

This Reviewer notes however, that demonstration of short-term safety and efficacy may not address the regulatory requirement for viral risk assessment which is the predominant focus of this Advisory Committee.

1.2.2 Clinical Background

Pancreatic enzyme products (PEPs) are used for treating patients PEI from causes such as CF, CP, and pancreatectomy. Patients with PEI 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 clinical practice, PEI is diagnosed by identification of clinical signs and symptoms (such as bloating, flatus, and large bulky stools) in patients with an appropriate history (e.g., known CF). Therefore, while some sources state that the gold-standard for establishing the diagnosis of PEI, severity of PEI, and magnitude of response to PEP therapy is documentation of a CFA before PEP treatment and during treatment, this may not reflect the state of clinical practice given the availability of PEPs and the ease with which symptoms such as improved weight and growth can be followed. In summary, PEP therapy is commonly begun in these patients with initial CF diagnosis and without documentation of a pre-treatment CFA.

The CFA is performed by having a patient consume a pre-determined amount of dietary fat and measuring the residual stool fat. The CFA, therefore, is an index of dietary fat absorption based on stool fat excretion. Healthy infants less than 6 months old have CFA >85% and healthy adults have CFAs >95%.⁴ Affected patients have varying amounts of residual fat resulting in lower than normal CFAs. Response to PEP therapy is determined by a decrease in clinical symptoms and an increase in CFA compared to pre-treatment. Treatment may increase CFA to near normal levels (for example, > 85%). In severely affected patients, such as patients with non-treatment CFA <40%, increases of >30% with treatment are generally believed to be clinically meaningful. Clinically meaningful increases in less severely affected patients have not been clearly defined.

Safe PEP dosing guidelines were established by the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA in the 1990s to reduce the risk of fibrosing colonopathy (FC), a serious and potentially life threatening condition that involves colonic stricture. Severe FC may result in colonic obstruction and require removal of some, or all, of the colon. FC has been implicated with high lipase doses.^{5, 6, 7}

⁴ Astra-Zeneca. First Principles in Gastroenterology, Web Edition, Chapter 7 Malabsorption. September. 2008.

⁵ Borowitz DS, Grand RJ, Durie PE, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatrics*. 1995. 127 (5): 681-684.

⁶ 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.

⁷ 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.

To minimize the risk of FC, the CFF has set guidelines for starting dose, titrating dose, and maximum dose.^{1,5,7} Dose is based on lipase concentration (lipase units; Lu). For children > 4 years of age and adults, dose is based on kilograms (kg) of body weight, and the starting dose is 500 Lu/kg/meal. If symptoms and signs of malabsorption persist, the dose may be titrated up to 2,500 Lu/kg/meal (or, 10,000 Lu/kg/day, based on 3 meals plus 2 snacks, where each snack counts as ½ of a meal). The risk of FC with doses above 2,500 Lu/kg/meal is unclear and these doses should be used with caution, and should be considered only after a thorough clinical and laboratory investigation rules out other treatable causes for clinical failure (e.g., lactose intolerance), and if the higher doses are documented to be effective by 72-hour fecal fat measures that indicate a significantly improved CFA compared to the lower dose. Doses above 6,000 Lu/kg/meal should not be used because the risk of FC outweighs potential benefit. Patients receiving doses >6,000 Lu/kg/meal should be examined and the dosage should be either immediately decreased or titrated downward to a lower range.

1.2.3 Regulatory History of Creon

Since 1993 the currently marketed product (CMP) has been in continuous distribution. The Applicant intends to replace CMP with the to-be-marketed product (TbMP). Comparability of CMP to TbMP has not been demonstrated.

The original NDA for Creon was completed in October-2003. The NDA application was not approved. The Applicant submitted a Complete Response (CR) in November 2006 (i.e., the 2006 CR) to address the deficiencies that resulted in the prior non-approval, which was also not approved.

The Applicant submitted the current CR in June 2008 (i.e., the 2008 CR). The 2008 CR contains clinical information from a single adequate and well-designed trial of TbMP in 32 patients with CF, ages 12 to 43 years (Study S245.3.126, the Pivotal Study). The submission also contains clinical information from 37 studies of CMP and 22 studies of PEPs other than Creon (e.g., other PEPs). The safety information from these 59 studies of non-TbMP formulations was similar to published data, with most adverse events due to primary disease, complications of primary disease, or unrelated causes. Therefore, these safety data may be used to support safety of the PEP drug-class and may contribute generally to the safety profile of the TbMP. However, since bridging of TbMP to non-TbMP formulations has not been demonstrated, a determination of approval relies predominantly on clinical data from the Pivotal Study. Therefore, for the purpose of this briefing document, only safety information from the Pivotal Study will be discussed.

1.3 Clinical Summary

1.3.1 Description of the Pivotal Study

The Pivotal Study was a 3 week, multi-center, randomized, double-blind, placebo-controlled, cross-over (CO) study of 32 patients with CF, ages 12 to 43 years. The study was performed with TbMP. Patients must have been on another PEP product at a stable dose for at least three months prior to Pivotal Study entry. Enrollees also needed evidence of PEI, proven by either a documented CFA <70% or fecal elastase <50 ug/gram stool in the prior year.

Creon dose was 4,000 Lu/gram dietary fat/day based on diet that met the caloric requirements of each patient, with 40% of calories derived from fat, and a minimum of ≥ 100 gram fat/day diet. The primary efficacy measure was the 72-hour CFA test. Efficacy was defined as the mean change in CFA [Creon minus Placebo] for the full analysis population (FAP), i.e., all patients who received ≥ 1 randomized dose who also had CFA assessments during both CO treatment periods. The mean change in CFA was 39% (95% C.I. 32, 46); $p < 0.001$ using ANOVA modeling with treatment, sequence, and cross-over period as fixed effect and patient within sequence as a random effect. The clinical review team concludes these results are clinically meaningful and statistically significant.

The short-term safety profile revealed no deaths, one withdrawal after Creon treatment due to weight loss $> 5\%$ within 3 months of Screening (violation of entry criteria), and two SAEs, duodenitis and gastritis, in a single patient two weeks after Creon treatment; the relationship of these SAEs to Creon can not be determined. Noteworthy clinical laboratory findings were restricted to decreased neutrophil counts in three patients during Creon treatment. There were no other clinically noteworthy findings.

There were no documented cases of FC in the Pivotal Study, which is not unexpected for several reasons. First, FC presents acutely but probably develops slowly over time; therefore, early cases might not have been recognized. Second, FC is a histopathologic diagnosis and the study was not designed to actively screen for FC with, for example, surveillance colonoscopy and biopsy. Lastly, dose and duration may not have been sufficient to precipitate FC.

1.3.2 Description of Other Clinical Information

The short-term safety of Creon is based on the Pivotal Study, which is the only randomized, double-blind, placebo-controlled trial of the TbMP. The integrated summary of safety (ISS) contains clinical information from 59 studies of non-TbMP formulations (CMP and other non-TbMP PEPs), the majority of which were reviewed during prior review cycles for this NDA. In general, the safety findings in these other 59 studies were similar to clinical findings published in open-source literature. Most adverse events were associated with primary disease processes, complications of primary disease processes, or unrelated causes such as trauma. The Reviewer notes that clinical data from these studies of non-TbMP formulations may, therefore, support safety of the drug-class and contribute indirectly to the safety profile of the TbMP. However, since in comparability (i.e., duodenal lipase activity) of TbMP and non-TbMP formulations have not been established, a determination of approval relies mainly on clinical data from the Pivotal Study. Therefore, for the purpose of this briefing document, presentation of clinical information is limited to a discussion of the Pivotal Study.

1.3.3 Summary

The clinical history of animal-derived PEPs supports the use of a single short-term adequate and well-controlled clinical trial using CFA to determine efficacy. Current Agency guidance recognizes the documented weight of clinical evidence demonstrating safety and efficacy for PEPs as a regulatory class across multiple disorders that exhibit PEI (e.g., CP or pancreatotomy).^{1, 2, 5, 7} In these patients, as in CF patients, efficacy is also assessed predominantly by clinical response to PEP treatment including improved growth and decreased abdominal symptoms, and can be supported by use of stool fat measurements such as CFA.

This Reviewer concludes that the Pivotal Study fulfills the regulatory requirements described in the PEP Guidance for evaluation of safety and efficacy for PEPs under NDA review. Therefore, this Reviewer concludes that from a clinical standpoint, the TbMP product could be approved to treat patients with PEI due to CF and other causes. Likewise, the safety profile in these patients is favorable with adverse events most commonly associated with primary disease processes, complications of primary disease, and unrelated complications. Therefore, FDA has determined that demonstration of safety and efficacy in a single adequate and well-controlled trial in CF patients could support an indication for use in patients with PEI due to multiple primary disorders.

A notable limitation of the clinical database of the TbMP is the lack of evaluation of safety and efficacy in children younger than 12 years old.

1.4 Summary

The information in this briefing document is intended to provide clinical background information for the Committee to deliberate on two issues: 1) risk assessment and mitigation of adventitious viruses (such as porcine parvovirus) including transmission of virus from this porcine-derived product; and 2) whether the product could be safely labeled for patients younger than 12 years of age who have not yet been studied using the TbMP.

The following discussion points are raised to the Advisory Committee:

1. FDA requests that the Advisory Committee discuss the safe use of Creon in children younger than 12 years old, given that the only completed randomized, placebo-controlled study of the TbMP product was in patients with CF, ages 12 years and older.
2. FDA requests that the Advisory Committee discuss the adequacy of the Applicant's viral assessment and risk-mitigation strategy (see questions in the Division of Therapeutic Proteins background information).

2 Detailed Background Information

2.1 Regulatory History of Porcine Derived PEPs

The only pancreatic enzyme products (PEPs) currently available in the US are marketed as nutritional supplements rather than drugs. The regulatory distinction between new drugs and nutritional supplements, in brief, is that new drugs may be approved for marketing if sufficient evidence is provided in a new drug application to establish the following: safety and efficacy of the drug for the labeled indication, consistent purity and potency of the drug, consistent adherence to good manufacturing, and accurate labeling. In contrast, nutritional supplements are generally classified as foods and the law does not generally require FDA review or approval prior to marketing. Each manufacturer is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading.

Since PEPs have been available in the US since before the enactment of the Federal Food, Drug, and Cosmetic Act (The Act) of 1938, and prior to the Drug Efficacy Study Implementation (DESI) requirements of 1962, the majority of currently available PEPs have not been developed under a clinical framework that would support an NDA and, as of October 2008, have not been submitted for NDA review. The only product that has received an FDA marketing approval is Cotazym® (sponsored by Organon, Inc); however, this medication is not currently marketed in the US. Therefore, no PEP is currently available to the US market under an approved NDA.

Of PEPs currently marketed as nutritional supplements, various dosage forms of pancreatic enzyme drug products are available as uncoated tablets, powders, capsules, enteric-coated tablets, and encapsulated enteric-coated micro-spheres. These formulations are not considered to be clinically interchangeable.

In the late 1980s and early 1990s, FDA assessed the appropriateness of marketing PEPs as over the counter drugs. As part of this endeavor, FDA evaluated the safety and effectiveness of then marketed PEPs, and noted the following issues across most or all products:

- Variation in bioavailability among similar dosage forms between manufacturers that could affect safety and efficacy.
- Variation in bioavailability within the same product from one manufacturer (e.g., lot to lot and within lot variability) that could affect safety and efficacy.
- The spectrum of diseases for which PEPs would be used, such as cystic fibrosis (CF), required chronic medical monitoring and necessitated a prescription only status.

FDA determined that these issues had a meaningful effect on safety and efficacy, necessitating new drug review of each product in order to standardize enzyme bioactivity. FDA also determined that since continuous physician monitoring of patients would be necessary for the safe and effective use of PEPs, these products should be available by prescription only. FDA

announced these decisions in the Federal Register on 28-April-2004, and subsequently published the PEP Guidance in the Federal Register of 14-April-2006, which is intended to provide regulatory assistance to manufacturers that plan to submit NDAs for PEP therapies. The framework outlined in the PEP Guidance was intended to address the development of animal-derived PEPs rather than PEPs developed through other methods such as cell-line derived (i.e., recombinant) products.

The 2004 FR notice also advised the public that FDA intended to exercise enforcement discretion (products would not be withdrawn from the market as misbranded new drugs) until 28 April 2008. This decision was made because FDA considered PEPs to be medically necessary and intended that PEPs should remain available to affected patients while manufacturers conducted the required studies, prepared and submitted NDA applications, and FDA completed thorough new drug reviews. The 2008 deadline was later extended to avoid an interruption in availability, and in October 2007, FDA announced its intent to continue exercising enforcement discretion until 28 April 2010 for products under active IND on or before 28 April 2008 and under NDA on or before 28 April 2009.

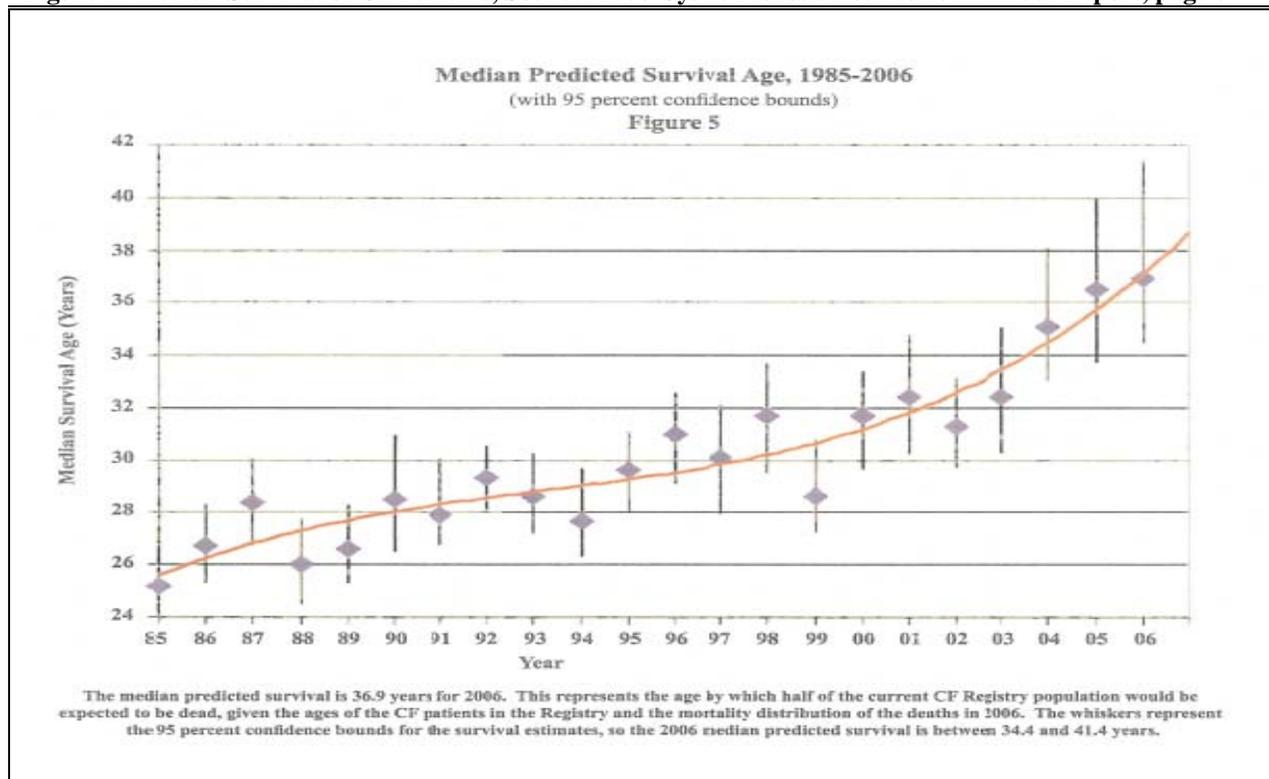
As noted in the PEP Guidance, PEPs have a generally well-described risk profile and are generally well tolerated. However, two recognized risks of PEP treatment include fibrosing colonopathy (FC) and hyperuricemia.^{4, 8} The cause of FC is unknown but it appears to be related to high daily lipase doses and use of extended release formulations, particularly in younger patients. With implementation of Cystic Fibrosis Foundation (CFF) dose guidelines, the incidence of FC has decreased.^{4, 6, 7} Hyperuricemia is due to the high purine content of porcine-derived PEPs, and these purines are converted to uric acid in the body. The PEP Guidance also recognizes the theoretical risk of transmission of adventitious porcine viruses, such as porcine parvovirus.

A direct correlation of PEPs with improved clinical outcomes is generally acknowledged in clinical practice but has difficult to demonstrate. However, the 2006 Cystic Fibrosis Foundation Annual reports that median survival of CF patients has increase from approximately 25 years in 1986 to approximately 37 years in 2006 (Figure 1).⁹ More significantly, recently published evidence based review shows that PEPs are associated with improved nutrition and that improved nutrition is associated with improved respiratory function and growth indices such as weight-for-height percentiles, and that these improvements are associated with improved pulmonary function and survival in adults and children.¹

⁸ Davidson GP, Hassel FM., Crozier D, Corey M, Forstner GG. Iatrogenic hyperuricemia in children with cystic fibrosis. *J Pediatr.* 1978 Dec;93(6):976-8.

⁹ Cystic Fibrosis Foundation Patient Registry 2006 Annual Data Report to the Center Directors, Bethesda, MD. www.cff.org.

Figure 1: Median Survival of CF Patients, Source: 2006 Cystic Fibrosis Foundation Annual Report, page 8.⁹



FDA accepts these data as supporting the efficacy and safety of PEPs as a drug-class. FDA also believes that the weight of this prior clinical evidence is of a sufficient magnitude that the safety and efficacy of a candidate PEP drug may be demonstrated by a single adequate and well-controlled, short-term study using CFA as primary efficacy endpoint. However, the following important regulatory issues were identified by FDA and are to be addressed for any marketed PEP:²

- To comply with the Pediatric Research Equity Act of 2003 (PREA) (21 U.S.C. 355c), the application must contain data that are adequate to assess the safety and effectiveness of the PEP for the claimed indications in each of the appropriate pediatric subgroups (newborns, infants, children and adolescents). The data should be adequate to support dosing and administration in each pediatric subpopulation for which the drug has been assessed to be safe and effective. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation can be supplemented with data to define dosing and safety for the relevant age groups.

- As with other animal-derived products, Applicants must perform full viral risk assessments and must show removal and/or inactivation of viral agents per the International Council on Harmonization (ICH) standards document Q5A.

2.2 Clinical Description of Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency (PEI) is a feature of multiple disorders of the pancreas. Cardinal features include malnutrition due to fat, protein, and carbohydrate malabsorption and gastrointestinal symptoms such as abdominal pain and bloating, and excretion of voluminous fat laden stools. Historically, nutritional treatment includes provision of exogenous PEPs, and of a high calorie diet with sufficient fat to replenish stool losses and maintain growth in appropriate age groups.

Two diseases characterized by PEI are CF and chronic pancreatitis chronic pancreatitis (CP).

CF occurs in approximately 1 in 2,500 live births in the US and there are currently approximately 30,000 CF patients in the US.^{9, 10} According to data reported by the Cystic Fibrosis Foundation (CFF), approximately 90% of patients with CF have PEI severe enough to warrant treatment with PEPs. In untreated children, progressive PEI and chronic pulmonary compromise result in growth failure. Improvements in nutritional, gastrointestinal and pulmonary care have resulted in improved health and increased long-term survival.

CP occurs in approximately 1 in 2,500 adults in the US and results from numerous etiological insults, most commonly consumption of alcohol or other toxins.¹¹ Progressive inflammation and destruction of pancreatic exocrine tissues results in deficiency of endogenous lipases, amylases, and proteases. The severity of CP varies and the percentage of these patients who require treatment with PEPs is unknown. Treatment with PEPs improves fat absorption and is associated with weight gain in these patients, though long-term outcomes are related to primary disease processes.

2.3 Coefficient of Fat Absorption (CFA) as a Clinical Endpoint

In clinical practice PEI is most commonly diagnosed by history and clinical symptoms, and response to therapy is documented by improved symptoms such as decreased abdominal complaint and decrease in the number and volume of stool. However, the gold standard for identifying PEI and the severity of PEI, and determining response to treatment is performance of a 72-hour coefficient of stool fat absorption (CFA) assessment.² This test is performed by feeding a patient a pre-defined amount of dietary fat, measuring the amount of stool fat excreted over 72 hours, to determine the percentage of fat absorbed by the body compared to dietary fat intake. CFA is expressed as a percent. The equation is summarized below:

¹⁰ Scriver CR., Beaudet AL, Sly WS, Valle D, et al. *The Metabolic and Molecular Basis of Inherited Disease*, 8th Ed., McGraw-Hill, NY USA. 2001; page 5121.

¹¹ Go VLW, Everhart JE. Pancreatitis. In: Everhart JE, ed. *Digestive Disorders in the United States: Epidemiology and Impact*. US Department of Health and Human Services, National Institutes of Health. Washington, DC: US Government Printing Office, 1994:691-712.

$$\frac{[(\text{Dietary Fat Ingested} - \text{Fat Excreted in Stool})] \times 100}{\text{Dietary Fat Ingested}}$$

Healthy infants less than 6 months old have CFA >85% and healthy adults have CFAs >95% (i.e., the body has the ability to absorb > 85 to 95% of the ingested fat in these ages groups), and severely affected individuals have lowest CFA values, for example CFA <40%. In affected individuals, treatment with exogenous PEPs increases the body’s ability to absorb dietary fat, with a commensurate increase in CFA. Common goals of therapy are to attain a treatment CFA \geq 80 to 85%. Increases of \geq 30% with treatment are commonly reported as being clinically significant in severely affected patients, such as patients with CFA with non-treatment CFA less than 40%.

FDA has concluded that it is appropriate to recognize CFA as an established efficacy parameter for the development of PEPs for treatment of PEI.²

3 Clinical Trial Design of the Pivotal Study (S25.3.126)

3.1 Introduction

The Applicant proposes the following indication for the TbMP formulation of Creon (Pancrelipase Delayed-Release Capsules)—hereafter referred to as Creon:

“Treatment of maldigestion in patients with exocrine pancreatic insufficiency”

The Applicant proposes individualized dosing according to the “degree of steatorrhea present and the fat content of the diet” with therapy to be initiated at the lowest possible dose and gradually increased until the “desired control of steatorrhea” is obtained.

Determination of efficacy is based on review of a single new Pivotal Study (S245.3.126), which was performed with TbMP. Study design is described in Section 4 of this document. Efficacy assessments are described in Section 5 of this document.

Determination of short-term safety is based on review of the Pivotal Study. Safety assessments are described in Section 6 of this document.

3.2 Study Design

The Pivotal Study was a three-week, multi-center, randomized, double-blind, Placebo-controlled, two-arm, cross-over (CO) study of Creon 24,000 Lipase unit (Lu) capsules and Placebo in patients with CF, ages 12 years and older. Patients must have been on stable doses of any other PEP treatment (prior PEP) for at least three months to qualify for enrollment. Diet was determined for each patient based on his/her caloric requirement, with 40% of the calories from fat, with a minimum fat intake of \geq 100 gram fat/day. Study Drug dose was 4,000 Lu/gram of dietary fat/meal. Patients who were on > 4,000 Lu/gram fat/meal on their usual PEP treatment prior to start of the study were given the same Lu/gram fat dose of Creon during the study. Patients were randomized 1:1 to either of the CO sequence: Creon→Placebo, or Placebo→Creon. Each CO treatment period lasted 5 to 7 days. Seventy-two hour stool collections for CFA analyses commenced on the evening of Day 2 of each CO period.

Treatment effect for each patient was defined as mean CFA obtained during the Creon treatment period (Creon CFA) minus mean CFA obtained during the Placebo treatment period (Placebo CFA); patients were their own controls. Thirty-four patients were screened, 32 patients received ≥ 1 dose of Placebo or Creon, and 31 patients completed all study procedures.

The two CO periods were separated by a three to 14 day washout period (WO). During the WO period treatment with Creon or Placebo was discontinued and patients resumed their prior PEP at their pre-study dose, and an ad lib diet.

Table 1 provides a schematic of the study procedures. On completion of Screening at Visit 1 (V1), patients continued prior PEP treatment until V2, 3 to 14 days later. At V2, Day 1 of CO1, patients were hospitalized and randomized to Creon→Placebo or Placebo→Creon indicating treatment for CO1→CO2, respectively. Randomized study drug treatment began on Day 1 of each CO period. Ingestion of the planned diet began on Day 1 and lasted for five to seven days during each CO period.

Stool collections for 72-hour CFA analyses began on the evening of Day 2 of each CO period.

Safety follow-up was performed within 7 days after V5.

Table 1: Pivotal Study Design

Screening Period	Cross-Over Period 1 (CO1); 7 Days Inpatient		Wash-out	Cross-Over Period 2 (CO2); 7 Days Inpatient		Follow-Up
Visit 1	Visit 2 (Day 1)	Visit 3 (Day 6 or 7)	3 to 14 days	Visit 4 (Day 1)	Visit 5 (Day 6 or 7)	One week after Visit 5
Screening procedures; Continue Prior PEP	Day 1 of DB treatment; Creon or Placebo	Complete 1st 72 hour CFA collection	Prior PEP; Regular diet	Day 1 of DB treatment; Placebo or Creon	Complete 2nd 72 hour CFA collection	Safety Follow-Up
	Study Diet Days 1 to 7. First stool dye given at end of Day 2 72 hr CFA start on the evening of Day 2			Study Diet Days 1 to 7. First stool dye given at end of Day 2 72 hr CFA start on the evening of Day 2		

Source: After Applicant’s Table 2; page 23 of the Clinical Study Report, NDA Volume 3 page 1,142.

There were two primary objectives: short-term efficacy of Creon by assessing the mean change in CFA [Creon minus Placebo], and short-term safety of Creon compared to Placebo.

Secondary objectives included mean change in coefficient of nitrogen absorption (CNA) [Creon minus Placebo], and changes in stool fat, stool weight, and clinical symptoms (stool frequency, stool consistency, abdominal pain, and flatulence). Since these are not endpoints that will support approval, they will not be discussed in this briefing document or presented by FDA at the Advisory Committee meeting.

3.3 Eligibility Criteria

Notable inclusion criteria are:

- Diagnosis of CF by either two sweat tests or genetic testing.
- Evidence of PEI documented by a CFA <70% without PEP supplement or a fecal elastase <50 ug/gram stool within one year of Screening.
- Patients 12 years or older.
- Treatment with prior PEPs at stable doses for ≥ 3 months prior to Screening.
- No more than a 5% loss in body weight within the 3 months prior to Screening.

Notable exclusion criteria are:

- Patients younger than 18 years old could not have a body mass index percentile <10%.
- Presence of acute or chronic illness at Screening thought to potentially interfere with safety or efficacy assessments.

3.4 Concomitant Medications

All patients must have been on prior PEP treatment at a stable (not defined) dose for at least 3 months prior to enrollment. Ingestion of PEPs other than Creon was not allowed during CO1 and CO2.

Medications affecting duodenal pH (e.g., H₂-receptor antagonists and antacids), gastric emptying (e.g., metoclopramide or erythromycin), or bile secretion (e.g., as bile acids or cholecystokinin [CCK] antagonists) were allowed if:

- The medication was commercially available and prescribed according to recommended dose.
- The medication was taken for >4 weeks before start of the study at the prescribed dose, and the dose could not change during the course of the study.

Prohibited medications during CO1 and CO2 included the following: nutritional supplements containing medium-chain triglycerides (MCT), narcotic analgesics, antidiarrheals (added by Amendment 2), antispasmodics (added by Amendment 2), laxatives, and immunosuppressive drugs (excluding steroids).

3.5 Visits and Procedures

Study visits and procedures are listed in Tables 2 and 3 below.

Table 2: Study Assessments; Screening, Crossover (CO), and Follow-Up (F/U) Visits

Study Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Safety F/U
Study Day	Day - 14 to -1	CO1 Day 1	CO1 Day 6 or 7	CO2 Day 1	CO2 Day 6 or 7	
Screening Procedures	X					
Physical examination, height	X		X		X	
Weight, vital signs	X	X	X	X	X	
Laboratory Tests	X		X	X	X	
Clinical Global Impression	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X
Symptom History	X			X		
Treatments and Assessments Within CO Periods	See Table 2					

Source: Table 3; page 30 of the Clinical Study Report, NDA Volume 3 page 1,149.

Table 3: Study Assessments During Crossover Periods

Study Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 or 7
Hospital Entry; Start Study Diet	X					
Dose Administered	X	X	X	X	X	
Compliance Assessed	X	X	X	X	X	
Stool Dye #1 Ingested; evening		X				
Record Diet Begins with Day 2 dye ingestion		X	X	X	X	
Stool Collection		X	X	X	X	X
Symptom History	X	X	X	X	X	
Weight	X	X	X	X	X	X
Stool Dye #2 Ingested; evening					X	
End Hospitalization						X

Source: Table 4; page 30 of the Clinical Study Report, NDA Volume 3 page 1,149.

3.6 Control, Blinding and Randomization

Blinding and control were established by use of Placebo that was designed to have similar appearance, smell, and taste to Creon.

Randomization was performed at the start of CO1 using central randomization. Patients were randomized using a centralized telephone activated voice response system. The randomization scheme was developed and implemented by the Applicant.

3.7 Study Medication Dose Selection

Caloric requirement was determined for each individual patients based on age, weight, and activity, and each patient was given a diet consisting of 40% of calories to be derived from fat, and consisting of at least 100 grams of fat/day. The drug dose was 4,000 Lu/gram of dietary

fat/day. Doses were to be administered over a three meal and two to three snack schedule. Snack doses were ½ the meal dose.

3.8 Efficacy and Endpoint Measures

The primary efficacy endpoint was change in mean CFA during the Creon treatment period minus mean CFA Placebo treatment period, where each patient served as their own control. As described in section 2.2 of this document, change in CFA is the gold standard for defining PEI and for response to treatment, and is the only efficacy endpoint upon which approval will be determined.

3.9 Safety Assessments

The safety population was all patients who received at least one dose of randomized treatment with Creon or Placebo (N=32).

Safety was assessed by noting the types and incidence of adverse events (AEs), deaths, discontinuations due to AEs, serious and severe AEs, changes from baseline in physical exams (including vital signs), and changes in clinical laboratory assessments including clinical chemistry, hematology and urinalysis. Physical examinations were performed at Screening and at the end of each CO period.

3.10 Adherence to Good Clinical Practices (GCP)

On review of a single interim Blinded Data Review (BDR) and its supporting documents, the clinical and statistical review teams concluded that the blind was not broken. No references to an independent data safety monitoring board (DSMB) were located in the study report; however, a representative of the Applicant's Quality Assurance Department was authorized to audit each site for adherence to regulatory requirements.

Data quality/integrity concerns were reported at one site with two patients. Both patients were dosed according to the investigator's judgment rather than by pre-specified dose (*ad hoc* dose) and the pre-specified meal plan was not provided. The review team concluded that the clinical data from this site was unreliable. However, the problematic data could be isolated and did not preclude assessment of the remaining data. Review of the clinical information from other study sites revealed no other notable data quality issues.

In conclusion, the overall study was conducted in adherence to GCP.¹²

3.11 Statistical Analysis Plan

The study was designed to demonstrate a >14% difference in CFA between Creon and Placebo with an estimated and standard deviation (SD) of 20%. The Applicant calculated that a sample size of 24 should have 90% power to detect an effect size of 0.7 using a paired t-test with a 0.05 two-sided level of significance. The Applicant estimated that 24 patients would need to complete the study. To allow for patient drop-outs, 26 patients were to be enrolled. Analyses

¹² Center for Drug Evaluation and Research: Guidance for IndustryE6 Good Clinical Practice: Consolidated Guidance. April 1996. <http://www.fda.gov/cder/guidance/959fnl.pdf>

were to be performed using ANOVA models with treatment, sequence, and period as fixed effects and patient within-sequence as a random effect.

4 Efficacy Review

4.1 Methods

Efficacy analyses were performed on the Full Analysis Population (FAP) of all patients who received at least one dose of Creon or Placebo and had CO period 1 and 2 CFA assessments (N=31). Sensitivity analyses were performed on a modified FAP that excluded the two patients with data integrity issues (N=29).

Safety analyses were performed on all patients who received at least one dose of Creon or Placebo (N=32).

4.2 Demographics

A review of the demographic data was performed to assess balance in baseline characteristics of the two treatment sequences.

Thirty four patients were screened, 32 patients received ≥ 1 dose of Placebo or Creon, and 31 patients completed all study procedures. Mean age was 22.5 (SD 7.1) years; median 22 years and range 12 to 43 years. Mean and median ages in the two treatment arms were similar. Median age in females was 18 years; range 13 to 38 years. Median age in males was 23.5 years; range 12 to 43 years. The overall gender distribution was 66% male and 34% female. Gender effects for severity of PEI in CF are not described in the literature and this imbalance is unlikely to affect interpretation of the study results. Enrollment was 100% Caucasian and analyses by race/ethnicity could not be performed.

Placebo period CFA is shown as an approximation of Baseline (non-treatment) severity; 31% of patients had Placebo period CFA $\leq 40\%$, and 69% of patients had Placebo period CFA $>40\%$.

Table 4: Demographics

Trait	Statistic	Creon→Placebo	Placebo→Creon	Total
Age (years)	N	16	16	32
	Mean (SD)	22.8 (6.5)	22.2 (7.8)	22.5 (7.1)
	Median	22.5	21.5	22.0
	Minimum/Maximum	12/38	22/43	12/43
Age Strata				
	N (%)			
12 to 18 y		5 (31)	6 (38)	11 (34)
>18 y		11 (69)	10 (62)	21 (66)
Gender				
	N (%)			
Male		9 (56)	12 (75)	21 (66)
Female		7 (44)	4 (25)	11 (34)
Race				
Caucasian	N (%)	16 (100)	16 (100)	32 (100)
Placebo CFA ^{1,2}				
	N (%)			
≤40%		7 (44) ²	3 (19)	10 (31)
>40%		9 (56)	13 (81)	22 (69)

Source: Table 7; page 50 of the Clinical Study Report; NDA Volume 3, page 1,169, and this Reviewer’s analysis for Placebo CFA ≤ or >40%.

¹Assessment rather than demographic characteristic. Used as a proxy for Non-Treatment Baseline.

²One patient withdrew after the first cross-over period.

4.3 Patient Disposition

Thirty two randomized patients (100%) received ≥1 doses, and 31 (97%) patients received ≥1 dose and completed all study procedures.

Patient 0016-00001 (Center 16, patient 1) was removed from the study during or at the end of CO1 due to inadvertent ingestion of stool CFA dye capsule at the wrong time and was re-randomized and completed the study as patient 0016-00003.

Patient 0031-00002 was withdrawn at the end of CO1 (after Creon treatment) for violation of entry criteria [weight loss ≥5% for the 3 month period preceding enrollment].

4.4 Dose Administered

4.4.1 Dose; Calculated Based on Lu/Gram Fat Ingested/Day

The mean dose of Creon (CO Days 3 through 5) was 4,166 Lu/gram fat/day; approximately 4% above the target dose (4,000 Lu/gram fat/day). Mean dose in the Creon→Placebo arm was 4,287 Lu/gram/fat day (7% above the target dose) and mean dose in the Placebo→Creon arm was 4,053 Lu/gram fat day (1% above the target dose). The administered dose approximated intended dose in both treatment arms (Table 5).

Table 5: Creon Dose; Lu/Grams Fat/Day; Mean (SD) Day 3 through 5

Treatment Sequence	N=31
Overall	4,166 (766)
Creon → Placebo	4,287 (679)
Placebo → Creon	4,053 (831)

The mean Creon dose in Lu/kg/day is presented for illustrative purposes since this is a common dose practice. The mean Creon dose (CO Days 3 through 5) was 11,019 Lu/kg of body weight (kg)/day which is around the upper limit of recommended daily dose according to the CFF Guidelines (Table 6).

Table 6: Creon Dose; Lu/Kg/Day; Mean (SD) Day 3 through 5

Treatment Sequence	Creon N=31
Overall	11,019 (3,435)
Creon → Placebo	11,704 (2,829)
Placebo → Creon	10,377 (3,838)

4.5 Analysis of Primary Endpoint; Coefficient of Fat Absorption (CFA)

The primary efficacy analysis was comparison of mean change in CFA [Creon minus Placebo] where each patient served as their own control. CFA values from Creon treatment in CO1 and CO2 were combined, and CFA values from Placebo treatment in CO1 and CO2 were combined.

4.5.1 Results

For the FAP, mean CFA during Creon treatment was 89% (SD 7), mean CFA during Placebo treatment was 50% (SD 18), and the mean difference in CFA was 39% (95% CI 32 to 46); p <0.001. The findings in the modified FAP were similar. The findings are clinically meaningful, statistically significant, and support efficacy (Table 7).

Table 7: Change in CFA (%) for Full Analysis and Modified Full Analysis Populations

	Creon	Placebo	Creon minus Placebo
Full Analysis Population			
n	31	31	
Sample Mean (s.d.)	89 (7)	50 (18)	
Adjusted Mean (s.e.)	89 (2)	50 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			39 (32, 46)
p-value for Adjusted Mean Treatment Difference			<0.001
Modified Full Analysis Population			
n	29	29	
Sample Mean (s.d.)	89 (6)	49 (18)	
Adjusted Mean (s.e.)	89 (2)	49 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			41 (34, 47)
p-value for Adjusted Mean Treatment Difference			<0.001

From FDA Draft Statistical Review (rounded to whole integer).

Source: Table 9 on page 54 and Table 3.1.1 on page 113 of Study S245.3.126 report. Full analysis population adjusted mean estimates are based on an ANOVA model with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Modified full analysis population adjusted mean estimates based on the Statistical reviewer’s analysis using a similar ANOVA model and without two subjects from Center 23.

A sensitivity analysis was performed by dose in Lu/gram fat/day (\leq or $>$ 4,000) because this is a commonly applied dose limit described in the CFF Guidelines. Mean CFA during Creon treatment in both groups was similar (86 to 90%) and mean increase in CFA was likewise similar (37 to 40%). A sensitivity analysis by dose in Lu/kg/day (\leq or $>$ 10,000) showed similar results (data not shown). Since this was single dosage study, base on a fixed dose per dietary fat, and

mean dose approximated the intended dose, failure to demonstrate a difference in response by dose was not surprising.

4.5.2 Exploratory Analysis by Placebo Treatment CFA

This Reviewer performed exploratory analyses by Placebo period CFA. Mean CFA during Creon treatment was similar (85 to 91%) irrespective of age or gender and in most patients was inversely related to CFA during Placebo treatment. There was no clinically meaningful difference in CFA with Creon treatment by age, gender, or Placebo-period CFA for either the FAP or the modified FA

Patients with lower non-treatment or Placebo CFA are expected to have a greater capacity to respond to PEP supplementation. Therefore, a sensitivity analysis of change in CFA by Placebo CFA [$>$ or \leq 40%] was performed.

In the FAP, patients with Placebo CFA \leq 40% had a mean CFA during Placebo treatment of 30% (SD 6) and a mean increase in CFA during Creon treatment of 60% (SD 4). Patients with Placebo CFA $>$ 40% had a mean CFA during Placebo treatment of 58% (SD 15) and a mean increase in CFA during Creon treatment of 30% (SD 15). Mean CFA during Creon treatment for the two groups was similar (90% and 88%). Results in the modified FAP were the same. The result is consistent with the expectation that patients with lower Placebo (no treatment) CFA have greater capacity to response to Creon treatment (Table 8).

Table 8: Sample Mean CFA by Placebo CFA

FAP (N=31)			
Placebo CFA \leq40%; n=9	Creon	Placebo	Creon minus Placebo
Mean (SD)	90 (6)	30 (6)	60 (4)
Median	90	30	61
Placebo CFA $>$40%; n=22			
Mean (SD)	88 (7)	58 (15)	30 (15)
Median	90	55	29
Modified FAP (N=29)			
Placebo CFA $>$40%; n=9	Creon	Placebo	Creon minus Placebo
Mean (SD)	90 (6)	30 (6)	60 (4)
Median	90	30	61
Placebo CFA \leq40%; n=20			
Mean (SD)	89 (7)	57 (15)	32 (15)
Median	91	55	30

In general, patients with lower CFA during Placebo treatment (\leq 40%) tended to have the greatest increase with Creon treatment (\geq 60%). This is illustrated in Table 9 which displays CFA for each patient (Placebo CFA, Creon CFA, and change in CFA). Patients are presented by in sequence by ascending Placebo CFA.

Table 9: CFA by Treatment for each Patient (N=31)

Treatment Period		Creon minus Placebo	Treatment Period		Creon minus Placebo
Placebo	Creon		Placebo	Creon	
23	84	61	47	92	45
23	82	59	51	78	27
23	84	61	51	81	30
29	91	62	54	93	39
30	93	63	55	96	40
32	90	59	58	88	30
32	96	64	64	87	23
38	98	60	67	93	27
40	90	50	67	82	16
41	90	49	68	95	27
41	94	53	72	93	21
42	93	51	72	97	24
43	72	29	77	84	7.3
43	80	37	83	78	-5
43	89	46	91	96	4.6
43	88	45			

4.6 Overall Efficacy Conclusions

In summary, short-term efficacy is based on demonstration of change (difference) in mean CFA (Creon minus Placebo) in the Pivotal Study of the TbMP. For the primary efficacy endpoint, change in CFA (Creon minus Placebo) for the FAP was 39% (95% CI 32 to 46); $p < 0.001$. These results are clinically meaningful and statistically significant. This Reviewer concludes that short-term efficacy of the TbMP has been demonstrated in patients with CF, ages 12 years and older.

Patients with Placebo CFA $>40\%$ had a mean increase in CFA of 30% (SD 15) with Creon treatment; patients with Placebo CFA $\leq 40\%$ had a mean increase in CFA of 60% (SD 4) with Creon treatment. Assessments by age and gender did not reveal clinically meaningful differences; across age groups and genders, mean CFA during Placebo treatment was similar (40% to 53%) and mean CFA during Creon treatment was similar (85% to 91%). The results suggest that patients with lower Placebo (no treatment) CFA have a greater capacity to respond to Creon treatment at a fixed dose, and that age and gender did not affect response.

5 Safety Review

5.1 Introduction

Short-term safety of Creon is based on the Pivotal Study, which is the only randomized, double-blind, placebo-controlled trial of the TbMP. Clinical information from studies of non-TbMP formulations may be used to support safety of the drug-class and may contribute generally to the safety profile of the TbMP. However, since bridging of TbMP to non-TbMP has not been demonstrated, a determination of approval relies mainly on clinical data from the Pivotal Study. Therefore, for the purpose of this briefing document, only safety information from the Pivotal Study will be discussed.

Safety analysis of the Pivotal Study was performed by noting the type and incidence of AEs. Deaths, SAEs, and withdrawals are reported from the signing of informed consent through completion of the final safety assessments approximately 1 week after completion of the 2nd cross-over period. Non-serious AEs are reported from time of first dose through completion of final safety assessments. Events that occurred during the washout (WO) period were designated as having occurred in association with the preceding controlled treatment (CO1).

5.2 Major Safety Results

5.2.1 Exposure

Mean duration of exposure to Creon was 5.1 days (SD 0.3).

Dose is described in section 5.3.2 of this document.

5.2.2 Deaths, Severe Adverse Events (SAEs), and Withdrawals

No deaths occurred in the Pivotal Study.

Two SAEs were reported in the Pivotal Study, both in Patient 0027-0001, a 12 year old boy in the Placebo→ Creon sequence who experienced duodenitis and gastritis approximately 2 weeks after his final Creon dose. He weighed 32 kg and his average daily lipase dose was approximately 5,727 Lu/kg/meal (note: this dose exceeded the maximum recommended CFF guideline dose of 2,500 Lu/kg/per meal). The case report form (CRF) was reviewed and the patient recovered without sequelae. The relationship of these SAEs to Creon can not be determined.

One patient was withdrawn. Patient 0031-00002 was an 18 year old female in the Creon→Placebo sequence. She was withdrawn on Washout (WO) Day 1, one day after her last Creon dose, due to weight loss >5% within three months prior to enrollment, which constituted a protocol violation. There were no other notable severe or serious AEs.

There were no documented cases of FC in the Pivotal Study, which is not unexpected since the duration of exposure (5 days) may not have been sufficient to elicit the outcome (FC).

5.2.3 Common Adverse Events

Overall, AEs during Creon treatment were similar in type to AEs during Placebo treatment, and AEs in both groups are generally representative of common complaints in the CF population. AEs were more common during Placebo (69%) than Creon (50%) treatment. The most common AEs during Creon treatment were abdominal pain and flatulence (9% each) followed by dizziness, headache, cough and nasal congestion (6% each). The most common AEs during Placebo treatment were abdominal pain, flatulence, and headache (25% each). The fewer AEs overall during Creon treatment likely reflects that Creon was efficacious in decreasing gastrointestinal symptoms. AEs occurring in ≥ 2 patients during the study are summarized in Table 10.

Table 10: AEs occurring in ≥ 2 Patients

System, Organ, Class	Preferred Term	Creon N=32	Placebo N=32
Gastrointestinal disorders	Abdominal pain	3 (9)	8 (25)
	Flatulence	3 (9)	8 (25)
	Abnormal feces	1 (3)	6 (19)
	Vomiting	1 (3)	1 (3)
	Abdominal pain upper	0	3 (9)
General disorders and administration site conditions	Pyrexia	0	2 (6)
Investigations	Weight decreased	1 (3)	2 (6)
Nervous system disorders	Dizziness	2 (6)	1 (3)
	Headache	2 (6)	8 (25)
Respiratory, thoracic and mediastinal disorders	Cough	2 (6)	0
	Nasal congestion	2 (6)	1 (3)
Patients with Any AE		16 (50)	22 (69)

5.2.4 Clinical Laboratory Assessments

The clinical laboratory dataset was thoroughly reviewed and changes in clinical lab findings that were classified as AEs were reported in the AE dataset.

Three patients with normal Screening absolute neutrophil counts (ANC; normal $>1,500 \times 10^3$ cells/uL) experienced potentially meaningful decreases in neutrophil count with Creon treatment. Patient 0031-00001 had a Baseline ANC of 7,640, which decreased to 620 with exposure to Creon in the first cross-over period and was normal from the end of WO (10,950) through the end of the study (6,860). This patient’s low ANC occurred concomitantly with a decreased WBC count (normal $<4500 \times 10^3$ cells/uL). This ANC meets the common clinical definition of moderate neutropenia (severe <500 , moderate 501 to 999, and mild $1,000$ to $1,500 \times 10^3$ cells/microL). Patients 0010-00007 and 0025-00002 had normal ANCs at Screening through CO1 (Placebo) and experienced decreased in ANCs during CO2 (Creon). Decreases in these two patients did not meet the clinical definition of absolute neutropenia (Table 11).

Table 11: Absolute Neutrophil and White Blood Cell (N/W) Count by Creon or Placebo (P) Treatment

Patient ID	Sequence	N/W	Screening	End of CO1	End of Washout	End of CO 2
0031-00001	Creon→P	N	7,640	620	10,950	6,860
		W	10,600	2,900	14,100	9,300
0010-00007	P→ Creon	N	4,430	3,530	4,470	1,570
		W	8,700	7,900	9,500	6,600
0025-00002	P→ Creon	N	5,920	7,760	3,610	1,660
		W	8,800	11,200	6,400	5,100

No clinically meaningful concomitant AEs were noted. The association of neutropenia with PEP treatment is not described in the literature and no explanation can be offered for these findings.

There were no other clinically meaningful clinical laboratory findings. Detailed serum uric acid analyses were performed because there is known dose-related risk of hyperuricemia and hyperuricosuria. However, there was no consistent difference in uric acid levels between Creon and Placebo.

5.2.5 Vital Signs

Changes in vital signs that qualified as AEs were reported in the AE dataset. An exhaustive review of the vital sign dataset was performed and there were no notable or consistent findings between Creon and Placebo treatment.

5.3 Overall Safety Conclusions

No deaths were reported, and no SAEs or withdrawals were attributable to Creon treatment. Adverse events in Creon- and Placebo-treated patients were similar in type and reflected common complaints in patients with CF. The higher incidence of adverse events in Placebo-treated patients is attributable to the higher incidence of gastrointestinal complaints in this group, likely reflecting lack of treatment.

Decreased neutrophil counts were seen in 3 (10%) patients during Creon treatment.

No cases of fibrosing colonopathy were reported; however, fibrosing colonopathy is diagnosed histopathologically and the study did not incorporate surveillance for this outcome into the study design (no colonoscopy or biopsy). Also, exposure in the current study may not have provided adequate stimulus. CFF dosing guidelines and the risk of fibrosing colonopathy should be addressed in labeling.

Hyperuricemia was not reported; however, the risk of hyperuricemia with PEP treatment is not disproved by the study. The risk of hyperuricemia should be addressed in labeling, however, as this has been highlighted in the medical literature.

In conclusion, except for neutropenia documented in three patients, the short-term safety profile of the TbMP demonstrated in the Pivotal Study is consistent with published literature. There were no other notable findings.

6 Summary

Short-term efficacy of the TbMP product was demonstrated in the Pivotal Study. The Pivotal Study was a randomized, double-blind, placebo-controlled study in 32 patients with CF, ages ≥ 12 years, who were dosed 4,000 Lu/gram of fat/day. The primary endpoint was the difference between mean CFA during Creon treatment minus mean CFA during Placebo treatment.

- The difference in CFA (Creon minus Placebo) for the full analysis population (FAP, N=31) was 39% (95% CI 32 to 46); $p < 0.001$. This Reviewer concludes these results are clinically meaningful and statistically significant. A sensitivity analysis showed that patients with Placebo CFA $> 40\%$ had a mean increase in CFA of 30% (SD 15) with Creon treatment, and patients with Placebo CFA $\leq 40\%$ had a mean increase in CFA of 60% (SD 4) with Creon treatment supporting the primary efficacy analysis and supporting the contention that magnitude of response (e.g., increase in CFA) with a fixed

dose is inversely related to baseline CFA; that is, more severely affected patients have a greater capacity to respond.

- Assessments by age and gender did not reveal clinically meaningful differences; across age groups and genders, mean CFA during Placebo treatment was similar (40% to 53%) and mean CFA during Creon treatment was similar (85% to 91%). The results suggest that patients with lower Placebo (no treatment) CFA have a greater capacity to response to Creon treatment at a fixed dose, and that age and gender did not affect response. Effects by ethnicity could be assessed because all patients were Caucasian.

In summary, this Reviewer concludes that short-term efficacy of the TbMP has been demonstrated in patients with CF 12 years and older.

The short-term safety of the TbMP formulation has been demonstrated.

- There were no deaths, SAEs, or withdrawals that were attributable to Creon treatment. Adverse events in Creon and Placebo treated patients were similar in type and reflected common complaints in patients with CF. The higher incidence of gastrointestinal AEs in the Placebo treated group likely reflected lack of treatment.
- No cases of fibrosing colonopathy were reported; however, the study was not designed to detect fibrosing colonopathy.
- Hyperuricemia was not reported; however, the hyperuricemia will be addressed in labeling, given the known risk that has been described in the medical literature.
- Prior review of the safety data from the 59 studies of non-TbMP formulations by this Reviewer revealed findings similar to published literature. In general, most adverse events were related to primary diseases, complications of primary diseases, or unrelated causes. These results may be used to support safety of the drug-class and may contribute generally to the safety profile of the TbMP.

In summary, short-term efficacy and safety of the TbMP of Creon have been demonstrated for the treatment of PEI in patients with CF, ages 12 and older. The development plan has broadly addressed the clinical requirements specified in the PEP Guidance. That is: an appropriate metric for efficacy was used (CFA); there was statistically significant and clinically meaningful improvement in the metric with PEP treatment in an appropriate population (CF); short-term safety was demonstrated; and the clinical data were demonstrated in the context of an adequately designed and well-controlled clinical study (e.g., randomized, double-blind, placebo-controlled). This Reviewer concurs with the PEP Guidance that PEI from different primary disorders has a similar clinical course and that the clinical findings in the Pivotal Study can support treatment of PEI due to other primary disease processes such as CP.

The most important clinical limitation in the clinical development plan is the lack of safety data with the intended to be marketed product in children less than 12 years old. This limitation is important since many children with CF are diagnosed in the newborn period and many of these

patients will require PEP treatment as infants. The Applicant plans two studies to assess safety and efficacy in younger children; one study is similar to the Pivotal Study and will evaluate children with CF from 7 to 12 years old; the other study will evaluate children with CF from one month through six years of age. The PEP Guidance states that clinical information from one pediatric age group may be used to support use in other age groups (extrapolation); however, while FDA in some instances permits extrapolation of efficacy, FDA does not generally permit extrapolation of safety.

Additionally, the Pivotal Study was not designed to address risk or risk-mitigation for transmission of adventitious porcine viruses, such as porcine parvovirus, with Creon treatment. These assessments are critical and will form a part of the regulatory decision process because is an animal (pig)-derived product.

7 Discussion Points for the Committee

1. FDA requests that the Advisory Committee discuss the safe use of Creon in children younger than 12 years old, given that the only completed randomized, placebo-controlled study of the TbMP product was in patients with CF, ages 12 years and older.
2. FDA requests that the Advisory Committee discuss the adequacy of the Applicant's viral assessment and risk-mitigation strategy (see questions in the Division of Therapeutic Proteins background information).