

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-725

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 30, 2009
From	Joanna W. Ku, MD, Acting Clinical Team Leader, DGP
Through To	Donna J. Griebel, MD, Division Director, DGP Julie G. Beitz, MD, Office Director, ODE III
Subject	Cross-Discipline Team Leader Review
NDA/BLA Submission	NDA 20-725 AZ
Applicant	Solvay Pharmaceuticals, Inc
Date of Submission	June 19, 2008; Received June 21, 2008
PDUFA Goal Date	Priority Review, December 19, 2008 With major amendment, March 20, 2009
Proprietary Name / Established (USAN) names	Creon® Pancrelipase
Dosage forms / Strength	Creon (pancrelipase) delayed release-capsules for oral administration, in USP units Creon 6,000 lipase/19,000 protease/30,000 amylase Creon 12,000 lipase/38,000 protease/60,000 amylase Creon 24,000 lipase/76,000 protease/120,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended:	Approval under CFR under 21 CFR 314

1. Introduction

This application is a Class 2 resubmission of Solvay's Complete Response (CR) to FDA's Approvable (AE) Action letter issued on August 16, 2007 for the Creon New Drug Application (NDA). Creon® is a pancreatic enzyme replacement product (PEP). The product is a gelatin capsule containing drug substance pellets that are enteric-coated with excipients to give it delayed-release characteristics. The active pharmaceutical ingredient (API) is pancrelipase, which is a combination of porcine-derived pancreatic enzymes consisting of lipase, protease, and amylase. Creon is available in 3 strengths, containing 6,000/19,000/30,000; 12,000/38,000/60,000; and 24,000/76,000/120,000, United States Pharmacopeia (USP) units of lipase/protease/amylase, respectively.

The Applicant's proposed indication was "for the treatment of maldigestion in patients with exocrine pancreatic insufficiency." Dosing regimens were proposed for four different patient populations: those with exocrine pancreatic insufficiency (EPI) due to 1) cystic fibrosis (CF), 2) chronic pancreatitis (CP), 3) post-pancreatectomy, and 4) other conditions. Dosing was to individualize based on the age of the patient, the fat content of the diet, the caloric needs to maintain good nutrition, and the amount needed to control steatorrhea. For patients with CF, regimen was to follow the Cystic Fibrosis Foundation (CFF) Guidelines, which are intended to minimize the risk of fibrosing colonopathy (FC), a serious condition that has been

associated with high doses of PEP.¹ Proposed labeling warnings included FC; (b) (4); irritation of oral mucosa; (b) (4); and hyperuricemia, which could worsen their conditions in patients with hyperuricemia, gout, or renal disease.

This application is for a new chemical entity (NCE). PEPs have been marketed in the United States, but without approval under New Drug Application (NDA). Creon brand capsules first became commercially available in the United States (US) in 1987 as Creon Microsphere capsules. The currently-marketed product (CMP), Creon Minimicrospheres®, first became available in the US in 1993, and has been marketed as a nutritional supplement. As of February 2009, the CMP has about (b) (4)% of the US market share. The Applicant intends to replace the CMP with the to-be-marketed product (TbMP), Creon, which is the subject of this review. Although both products contain the same active pharmaceutical ingredient (API), pancrelipase, the TbMP is distinguishable from the CMP by several characteristics, including 1) overage has been eliminated to allow more accurate lipase dosage labeling, 2) dibutyl phthalate has been removed from the formulation in response to recent global debate concerning the safety of alkyl phthalate, and 3) mineral oil has been removed because of concern that it might inhibit absorption of key nutrients, including fat-soluble vitamins. Additionally, the raw material for the CMP and TbMP is obtained from different sources and is subject to different manufacturing processes. Comparability of the two products has not been established, and therefore they are not considered interchangeable.

Because the Applicant did not conduct and has not obtained a right of reference to the studies in the medical literature that provided evidence for the long-term efficacy and safety of pancreatic enzyme products, or for the pharmacology-toxicology studies for the individual excipients to support the application, this NDA was submitted as a 505(b)(2) application.

The regulatory history and prior evaluation of the product have been summarized in the CDTL Review (July 31, 2007) by A. Pariser². This memorandum documents my concurrence with the Review Team's recommendation to approve Creon (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. Issues discussed in this document will focus on the new information that has been submitted in this CR, including the results of the single pivotal clinical study (the Pivotal Study) that was conducted using the TbMP, resolution of the manufacturing issues that were cited as deficiencies in the 2007 AE Letter, the Advisory Committee's deliberation regarding porcine product-related viral infection risk monitoring and mitigation plans, labeling and phase 4 activities negotiations, and FDA's response to the Citizen's Petition submitted by Eurand Pharmaceuticals, Inc, a competing manufacturer for another PEP.

¹ Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127:681-684. Please also see Appendix.

² Pariser, A. CDTL Review of NDA 20-725, July 31, 2007.

2. Background

Clinical Background

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. Any condition that disrupts the production of exocrine pancreatic enzyme can lead to EPI. Cystic Fibrosis (CF) is the most common cause in children, and chronic pancreatitis (CP) is the most common cause in adults. Symptoms include steatorrhea, abdominal pain, weight loss, and nutritional deficiencies due to malabsorption. Clinical stigmata include retarded growth and development, impaired immune response, infections, and bleeding tendencies. The mainstay of therapy has been the administration of exogenous PEP as enzyme replacement therapy (ERT).

The porcine pancreatic enzymes in Creon are lipases (herein identified as lipase), proteases and amylase, which catalyze the hydrolysis of fats to monoglycerol, glycerol and fatty acids, protein into peptides and amino acids, and starch into dextrans and short chain sugars, respectively. PEP is widely recognized as a medically necessary product and an essential component in the overall treatment strategy of EPI. It has been used in the US for +70 years, and there is a large body of literature to support the long term safety and efficacy of PEP as a class.

Pancrelipase is not systemically absorbed and the site of mechanism of action is at the duodenum and the proximal small intestine. Pancrelipase is intended to be taken when a patient eats a meal or a snack; therefore, the daily dosage and cumulative dosing requirement is significant over the course of this life-long therapy. An important safety issue regarding PEP use is fibrosing colonopathy (FC). The etiology of FC has not been definitely established, but has been associated with high dose lipase exposure. FC has also been thought to be possibly associated with excipients, or the underlying disease. The Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, has established consensus guidelines (CFF Guidelines) to limit the maximum daily dose to optimize efficacy while minimizing the risk of FC from high doses.^{3,4,5,6} Reports of FC in the literature have decreased since the publication of dosing guidelines in the 1990's.

Regulatory History of Pancreatic Enzyme Products (PEPs)

Regulatory history of PEPS

The regulatory history has been summarized by A. Pariser,⁷ and highlights are included as below. PEPs are currently widely available in the US as non-prescription nutritional

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

⁴ Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, *J Pediatrics* 1995; 127:681-684.

⁵ 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." <<http://www.fda.gov/cder/guidance/6275fnl.htm>> April 2006.

⁶ 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.

⁷ Pariser, A. CDTL Review of NDA 20-725, July 31, 2007.

supplements and over-the-counter (OTC) medications, or by prescription. Except for Cotazym®, no PEP has undergone FDA evaluation under Investigational New Drug (IND) applications or has had an NDA approval, because PEPs have been available since prior to the Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938, and most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI; pre 1962). If Creon is approved during this review cycle it will be the first currently marketed PEP in the US to be under an approved NDA (Cotazym is not a marketed product).

Among the currently marketed products, there are substantial variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (from lot to lot and even within lots). The FDA deemed that such product variability could adversely affect the safety and effectiveness of the PEPs. The Agency also considered that since continuous physician monitoring of patients would be necessary as a collateral measure to ensure the safe and effective use of these products, PEPs should be available by prescription only. In a *Federal Register* notice published on April 28, 2004 (69 FR 23410), FDA announced that all PEPs are to be considered new drugs, and that manufacturers who wish to continue to market PEPs must submit NDAs. Under the FD&C Act, new drugs are required to be the subject of approved NDAs. However, FDA determined that because prescription PEPs are medically necessary, the Agency will exercise enforcement discretion to allow manufacturer 4 years (until 2008) to obtain an approved application.

Because many manufacturers were experiencing delays in complying with the NDA regulations, in a *Federal Register* notice published on October 26, 2007 (72 FR 60860), FDA extended the original deadline to allow companies additional time (2 more years) to prepare and submit NDAs without interruption in commercial availability. FDA stated that it will exercise its enforcement discretion with respect to unapproved PEPs until April 28, 2010, if the manufacturers have INDs on active status on or before on or before April 28, 2008 and have submitted NDAs on or before April 29, 2009.

The PEP Guidance

In April 2006, FDA published Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs⁸ (the PEP Guidance) to assist manufacturers of PEPs in preparing and submitting NDAs.

Because FDA accepts that there is adequate evidence to support safety and efficacy of PEPs as a drug class, the requirements for the drug development program are unique for the class. For example, a PEP drug development program could rely on a single adequate and well-controlled study to demonstrate safety efficacy, but patient populations should include at a minimum an efficacy study in pediatric patients with CF. Meaningful endpoints could be pharmacodynamic measures such as decrease in steatorrhea as evaluated in a 72-hour quantitative stool collection. Study design could be a randomized, two-period, placebo-controlled, crossover study in as few as 10-25 patients with CF, and the duration of the entire

⁸ 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.” <<http://www.fda.gov/cder/guidance/6275fnl.htm>> April 2006.

trial could be days to 2 to 3 weeks. As to be discussed in this document, the Applicant's pivotal study met all of these criteria.

The Guidance also states that to be approved, an NDA must meet certain CMC requirements, including, 1) the manufacture process for the drug substance should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A. A full viral risk assessment should be made and justified.⁹ 2) Since high doses of PEPs have been associated with safety issues, the finished drug product should be formulated to 100 percent of the label-claimed lipase enzyme activity, i.e., that there should be no overage.

Per the Guidance, no toxicology studies are needed if excipients are classified as Generally Regarded as Safe (GRAS) for oral administration, or if they are United States Pharmacopeia–National Formulary (USP–NF) compendial excipients and are present at levels previously found acceptable. No new pharmacology studies are necessary because of the extensive use of the currently marketed PEP products; however, the Applicants should summarize the published literature about the pharmacology of their particular PEP.

Regulatory History of Creon

The original IND for Creon Minimicrospheres (the CMP) was opened in March 1995, and the NDA submission was opened on July 31, 1997. The Application was placed under Application Integrity Policy (AIP) on September 24, 1997 for data integrity issues, which suspended the review. The Applicant prepared and implemented a Corrective Action Operating Plan; the AIP status was revoked on April 9, 2003, and FDA resumed review of the NDA. Upon its completion, a Not Approvable (NA) decision was issued on October 19, 2003, based on deficiencies in Chemistry, Manufacturing, and Controls (CMC) and the lack of bridging between the TbMP with the other formulation(s) used in the clinical trials up to that point.

On November 20, 2006, FDA received the Applicant's Complete Response (herein identified as "the 2006 CR") to the 2003 NA letter. FDA issued at the end of the review of the 2006 CR, an Approvable (AE) Action (August 16, 2007), in which FDA stated that before the application can be approved, the Applicant will need to address a list of CMC deficiencies, including viral control and viral infection risk mitigation plans, and will need to conduct a clinical study in the TbMP, given that the duodenal bioavailability study submitted in the 2006 CR failed to establish clinical comparability between the CMP and the TbMP.

This current application (submitted on June 19, 2008) is a Class 2 resubmission of Solvay's Complete Response (herein identified as "the Present CR") to the 2007 AE Letter. A major amendment was received to this submission on December 5, 2008, which extended the PDUFA goal date to March 20, 2009. An Advisory Committee meeting was convened on December 20, 2008 to obtain advice from the Committee regarding efficacy, safety, and indication of Creon in the context of the theoretical risks of viral transmission from the product to treated patients, and to discuss viral risk monitoring and mitigation plans. Six

⁹ This provision refers to the risk assessment and mitigation of viral transmission from a porcine-derived product. It does not refer to PEPs that are derived through other methods such as cell-line derived or recombinant products.

weeks prior to the PDUFA extended goal date, on February 6, 2009 Eurand Pharmaceuticals, Inc. submitted a Citizen Petition to petition the FDA to address their concerns regarding the trade name, packaging, trade dress, sales, marketing and labeling for the Applicant's TbMP. The NDA review time was further extended to April 30, 2009 in order to sufficiently address the Petitioner's concerns.

The documents which have been consulted in writing this memorandum include the following. This memorandum summarizes selected information from the review documents and they should be consulted for more specific details.

Clinical Reviews by E. Hausman, dated April 30, 2009.
Cross Discipline Team Leader Review by A. Pariser, dated July 31, 2007.
Deputy Office Director Memo by D. Shames, dated August 16, 2007.
Statistical Review by S. Castillo, dated November 14, 2008
Clinical Pharmacology Review by T. M. Chen dated November 10, 2008.
Pharmacology/Toxicology Review by D. Joseph, dated November 18, 2008, and March 20, 2009
Chemistry Review by W. Guo, dated March 3, 2009.
DTP Chemistry (Virology) Review by E. Guan, dated March 20, 2009.
DSI Clinical Inspection Summary by K. Malek, dated December 3, 2008.
DMEPA Proprietary Name, Label and Labeling Review Consult, Response to Citizen Petition FDA-2009-P-0059 by Deveonne Hamilton-Stokes, dated March 27, 2009
DDMAC Labeling Memo by S. Doshi, dated November 24, 2008.
DRISK Patient Labeling and Education Team memo by S. Mills, dated January 28, 2009.
DRISK Review of Proposed REMS by J. Duckhorn, dated March 6, 2009.
PMHS Pediatric Consult Review by F. Collins, dated February 13, 2008.
FDA Briefing Material and Transcripts of the Antiviral Drugs AC Meeting on December 2, 2008.
DGP Response Memorandum to Citizen Petition FDA-2009-P-0059, dated April 29, 2009

3. CMC

For the present CR, CMC data have been reviewed in the Chemistry Review by W. Guo, dated March 3, 2009, and Virology Review by E. Guan, dated March 9, 2009. Both reviewers are part of the Division of Therapeutic Proteins (DTP).

Chemistry

The drug substance (DS) is a crude mixture of pancreatic digestive enzymes, principally lipases (b) (4) α amylase, and proteases (b) (4) The DS is prepared from (b) (4) porcine pancreas tissue from pigs raised as human food (b) (4)



The end product is the TbMP drug product (DP), Creon, and it is manufactured by Solvay. Pancrelipase is the United States Adopted Name (USAN) for the active pharmaceutical ingredient (API) in Creon. Creon is available in 3 strengths, labeled to contain 6,000/19,000/30,000; 12,000/38,000/60,000; and, 24,000/76,000/120,000 United States Pharmacopeia (USP) units of lipase/protease/amylase per capsule. The capsules are packed in HPDE bottles, which are then individually packaged in aluminum foil pouches for moisture protection to prevent disintegration of the pancrelipase (particularly, lipase) activity. Lipase activity is quickly lost by exposure to moisture and temperatures above 40° C.

The DS for the CMP is manufactured by Scientific Protein Laboratories, Waunakee, WI, and the DS for the TbMP is manufactured by Solvay Pharmaceuticals.¹⁰ Therefore the source materials for the two drug substances are different, and the different DS are also subject to different manufacturing processes.¹¹ The TbMP is also distinguishable from the CMP by several important characteristics. In the TbMP, 1) overage has been eliminated to allow more accurate lipase dosage labeling, 2) dibutyl phthalate because it is a reproductive and developmental toxicant in animals, and 3) mineral oil has been removed because of concern that it might inhibit absorption of key nutrients, including fat-soluble vitamins, and its removal is consistent with the requirements of 21 CFR 201.302. Comparability has not been established, and therefore these two products are not interchangeable. Overall, the TbMP is intended to be a safer and efficacious product that is produced with greater manufacturing consistency.

The following deficiencies were cited in the 2009 AE Letter: additional information was required on 1) the control of co-lipase activity in the DS and DP; 2) consistency in the fatty acid substrate used in the lipase potency measurements; 3) performance of dissolution testing of the DP using intact capsules; 4) definition of the acceptance criterion of the High Performance Liquid Chromatography (HPLC) identity test used for the DS and DP; 5) provision of the DS and DP release test sampling plans; 6) establishment of the acceptance criterion of lipase activity for individual capsules tested expressed as a percentage of the labeling claim; 7) information on the manufacturer and specifications of the container, closure, and seals for the DS packaging; and, 8) provision of representative certificates of analysis of the seals used in the DS container/closure system. The Present CR addressed all of these deficiencies adequately. Also, during the course of the review cycle, the Reviewer requested additional CMC information, which the Applicant addressed satisfactorily.

¹⁰ The swine sources for the TbMP are France, Germany, Portugal, Spain, the Netherlands, and the US.

¹¹ For a detailed summary of the manufacturing process differences between the CMP and the TbMP, refer to the Appendix of DGP's Response Memorandum to Eurand's Citizen Petition.

The CMC reviewer concluded that Creon is manufactured consistently, resulting in a safe and effective product that meets its expected quality parameters. Indeed, the purpose of bringing PEPs under NDA was to ensure standardization in manufacturing processes from batch to batch of these products. The Reviewer and the Division of Therapeutic Proteins (DTP) recommend approval from a product perspective. Storage instructions with regards to protection from high temperature and moisture conditions should be included. A statement that Creon is not interchangeable with any other pancrelipase product should also be included in the labeling.

Virology

See the Chemistry Review by E. Guan, dated March 20, 2009, and FDA AC Meeting briefing package.

Because Creon is produced from native porcine pancreas, the risk of contamination of the starting material with swine viruses that are capable of infecting humans was assessed. Because these products have a long history of use and have not been shown to transmit infectious disease, the risk was viewed as theoretical rather than actual. Nevertheless, there is a lack of compelling data indicating that the risk from adventitious viruses is insignificant, and the ability of infectious disease agents to cross species barriers has been long recognized as a possible danger to humans. An AC meeting was convened to address these issues with the public and to obtain advice from the experts.

The range of viruses that are known to infect swine can be categorized as enveloped or non-enveloped viruses, with the non-enveloped viruses being more resistant to physico-chemical inactivation by manufacturing control process. Swine viruses were also assessed in terms of risk from being known zoonotic (i.e., transmissible to humans, e.g., influenza A and hepatitis E virus), or potentially-zoonotic (i.e. known to harbor in swine but have yet been found to infect humans but may have the potential to cross species barrier to infect humans, e.g., porcine parvovirus). DTP stated that risk levels are different depending on whether a virus is enveloped vs. non-enveloped, and also whether it is known to be zoonotic vs. possible-zoonotic. These graded levels of risk required different levels of risk mitigation strategies.

In the Approvable (AE) Action (August 16, 2007), FDA stated that before the application can be approved, the Applicant needed to address the issues regarding viral control and viral infection risk mitigation plans, including 1) providing information on potential enveloped viral loads, and providing an overall assessment on the ability of the manufacturing process to effectively control this level of viral load, and 2) establishing specifications for the presence of infectious porcine parvovirus, or providing compelling evidence that the manufacturing process is capable of controlling the level of porcine parvovirus in the final product. The Reviewer found that the data submitted in the current CR adequately address these issues. The data showed that Solvay's manufacturing process is relatively robust and is capable of providing (b) (4) logs inactivation of enveloped viruses (but has a limited capacity to inactivate non-enveloped viruses). Therefore, additional controls (specifications and action limits) have been put in place by the Applicant to monitor certain zoonotic viruses and viruses that pose a risk due to the potential to change species tropism. For example, audit procedures have been put in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption, and to ensure that legal requirements regarding hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. The Applicant updated the porcine parvovirus genomics and infectivity

data, as well as proposed routine testing for porcine parvovirus on every batch by infectivity assay with a specification not more than (b) (4) grams. The Reviewer felt that although the proposed infectious assay for porcine parvovirus is not very sensitive, given that the virus has not found to infect humans, and a low level of live PPV is present in about 5% of the DS batches, which is independent of the assay sensitivity, the Applicant's response with regards to the porcine parvovirus issue is adequate.

The Reviewer proposed and the Applicant agreed to conduct a number of post-marketing requirement (PMR) and commitment (PMC) studies to ensure that the manufacturing process is well controlled regarding the risk associated with adventitious viruses, and that risk be further assessed after the approval (see Section 13 Recommendations/Risk Benefit Assessments for details). The Reviewer stated that labeling of all swine-derived PEPs, including Creon, should provide warning on potential viral exposure from the product source. The Reviewer and the Division of Therapeutic Proteins (DTP) recommended approval from a viral safety perspective.

Facilities review/inspection

A pre-approval and Good Manufacturing Practice (GMP) inspection of the manufacturing facility in Germany was conducted at the request of the Division of Field Investigations (DFI) and DTP. Approval was recommended.

4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology Reviews by D. Joseph, dated November 18, 2008, and March 20, 2009 for complete information.

General non-clinical pharmacology/toxicology considerations

Excipients are of particular concerns to PEPs because patients require daily ingestion of a large quantity of product to achieve adequate digestion. Consistent with the Guidance, review of pharmacology/toxicology in the 2006 CR was limited to the evaluation of the excipients breakdown product o-phthalic acid (IUPAC name, phthalic acid). The presence of phthalic acid in Creon is due to degradation of the excipient hydroxypropyl methylcellulose phthalate, and the amount of phthalic acid present was shown to increase during storage of the drug product.¹² Based on the results of the submitted studies and the summary report of other preclinical studies of phthalic acid, the information was deemed to be adequate to support the safe use of Creon in humans even at the estimated maximum dose. For the other TbMP excipients that are present in the CMP (Creon Minimicrospheres), the previously reviewed safety information provides a reasonable assurance of safety. All nonclinical studies were reviewed in the pharmacology/toxicology reviews from the first and second review cycles.

There are no new information submitted with the Present CR, and the review was limited to the proposed labeling in Sections 1 (Indications and Usage), 8.1 (Pregnancy), 12.1

¹² Note: The excipient hydroxypropyl methylcellulose phthalate has not been reported to be a reproductive and developmental toxicant in animals, unlike certain phthalic acid esters such as dibutyl phthalate. Hydroxypropyl methylcellulose phthalate (and its degradants) are not thought to be linked to any health concerns.

(Mechanism of Action), 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility). From a preclinical view point, the application could be approved with the provision that the labeling be changed as recommended. The Reviewer stated that because the CMP and the TbMP are not considered comparable, preclinical data using the CMP should not be included in the TbMP labeling.

5. Clinical Pharmacology/Biopharmaceutics

See the Office of Clinical Pharmacology Review by T.M. Chen dated November 10, 2008 for complete information.

In the 2006 CR review it was concluded that the *in vivo* duodenal intubation bioavailability study (S245.2.003) did not demonstrate comparability between the CMP and the TbMP.¹³ Furthermore, several non-compliance issues found by the Division of Scientific Investigation (DSI) for the study and analytical sites rendered the study unreliable. The Applicant was informed that since bridging failed, a clinical study using the TBM formulation would be required to support approval of the TBM.

Additionally, in the 2006 CR Amendment, the *in vitro* stability study using Creon pellets when mixed with acidic food was found to be inadequate due to methodological flaws in the study design. The Applicant was requested to perform a new *in vitro* stability study using the Agency's proposed study design to demonstrate stability of the DS in different pH environments. The study results were submitted as part of the Present CR.

When enteric coated pellets were tested with foods with pH <4, % recovery of lipase was stable, but with pH > 4, the % recovery of lipase decreased. This is consistent with the intended stability profile of enteric coated pellets, which is designed to remain stable in the acidic environment of the stomach during transit to the more basic environment at the site of action in the duodenum and the proximal small bowel. Based on these results, the Reviewer recommended that labeling should reflect that when swallowing of capsules is difficult and the capsules need to be opened to sprinkle the pellet contents to be mixed with food, the DS pellets should be mixed with acidic soft food with a pH of 4 or less, such as apple sauce, at room temperature, to maintain its stability. Creon should not be crushed or chewed, or mixed in foods having a pH greater than 4 because these actions can disrupt the protective enteric coating resulting in early release of enzyme, irritation of oral mucosa, and/or loss of enzyme activity. For example, contents of the capsule should not be mixed directly into formula or breast milk, as this might disrupt its dissolution integrity. In the Medication Guide, patients/parents should be instructed that care should be taken to ensure that the entire administered dose is swallowed and not retained in the mouth, to avoid irritation of the mouth.

Other issues

The Reviewer recommended deleting the Applicant's proposal labeling for Section 12.2 Pharmacodynamics because there is insufficient data to support the claim (b) (4)

¹³ As the Division has gained additional experience reviewing these clinical bioequivalence studies, it has become apparent that high inter-subject variability makes this type of study (which is recommended in the PEP Guidance) impracticable for establishing bioequivalence between two PEPs.

(b) (4)

Conclusion

The Reviewer recommended approval, provided that labeling will be revised to reflect the stability study findings.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Creon is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

The reader is referred to the Clinical Review by E. Hausman dated April 30, 2009 and the Statistical Review by S. Castillo dated November 14, 2008 for complete information.

The substantial evidence for efficacy in this application came from the Applicant's single pivotal study conducted in the TbMP that demonstrated improvement in fat absorption with Creon treatment over placebo.

Phase 3 Study – S245.3.126 (Pivotal Study)

The single Phase 3 study conducted in the TbMP was a randomized, double-blind, placebo-controlled, multicenter studies in 32 patients with exocrine pancreatic insufficiency due to CF, ages 12 to 43 years. The 10 study sites were in the U.S. Patients were treated with both Creon (Creon 24,000) and Placebo, each for a week in a cross-over study design. Patients were randomized 1:1 to either sequence: Creon→placebo, or placebo→Creon. Each patient served as their own control.

Eligibility, treatment, and assessments

To be eligible, patients needed to be older than 12 years of age, have a historically confirmed diagnosis of CF and EPI, and must have been on another PEP at a stable dose for at least 3 months prior to study entry. Patients were excluded for known allergy to PEP products, low body weight for pediatric patients, and a history of medical conditions that would interfere with the interpretation of the study results (including history of FC, distal ileal obstruction syndrome (DIOS) or acute pancreatitis within 6 months of enrollment, bowel surgery other than appendectomy or minor resection due to meconium ileus, celiac disease, or gastrectomy).

Study medications were taken with meals. Total daily dose was divided among meals and snacks. Patients were placed on a high-fat diet, as recommended by the CFF for CF patients. The administered lipase dose of the study drug was calculated by determining the caloric requirements of each patient based on age and weight; and, 40% of the calories had to come from fat, with a minimum daily fat intake of 100 grams. Drug dose was 4000 USP units of

lipase per gram of fat intake/day, which is within the dosing guideline in accordance with the CFF Consensus Conference.¹⁴ Placebo was dosed similarly. The calculated number of capsules per day was given in divided doses according to the fat content of each meal and snack.

Concomitant therapy (including H2-receptor blockers, antacids, sucralfate, proton pump inhibitors, metoclopramide, bile acids, cholecystikinin antagonists, etc.) that influence duodenal pH, gastric emptying, or bile secretion--all of which may alter the stability and release of lipase activity--were allowed only if they had been taken by the patient for more than 4 weeks before start of the study at the prescribed dose. Nutritional supplements containing medium-chain triglycerides, narcotics, anti-diarrheals, antispasmodics, laxatives, and immunosuppressive drugs (excluding steroids) were prohibited.

Patients were randomized 1:1 to either of the cross-over treatment sequence group: Creon→placebo, or placebo→Creon. Each cross-over period lasted approximately a week and patients were treated in an inpatient setting to ensure compliance. Patients were on the study drug for approximately 5 days. A 72-hour (3-day) stool fat testing commenced on Day 2 of each of the cross-over treatment period. On Days 3-5 of both cross-over treatment periods the same diet was given to the subject. The cross-over periods were separated by 3 to 14 days of washout period in an outpatient setting, during which patients could resume their prior PEP treatment at their pre-study PEP dose, along with an ad lib diet.

Study visits were conducted at screening (visit 1), beginning of the first cross-over period, (visit 2), end of the first cross-over period (visit 3), beginning of the second cross-over period (visit 4), end of the second cross-over period (visit 5), and a week after the second cross-over period for safety follow up (Visit 6). Physical exam and laboratory testing were performed, and adverse events and concomitants medication-use were collected throughout the study (table electronically copied from the Clinical Review).

Screening Period	Cross-Over Period 1 (CO-1); 7 Days Inpatient		Wash-out	Cross-Over Period 2 (CO-2); 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. 72 hr CFA start on the evening of Day 2.			Study Diet Days 1 to 7. 72 hr CFA start on the evening of Day 2.		

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

¹⁴ See Appendix 1 for CFF Consensus Conference dosing guidelines. The guidelines were established in conjunction with FDA. Per the guidelines, individual patient dosing should be titrated to clinical needs, but not to exceed 4000 lipase units/gram of fat ingested per day. In the Pivotal study, all patients were uniformly dosed at this maximum dose of 4000 lipase units/g of fat ingested per day.

Endpoint

The primary endpoint was the 72-hour coefficient of fat absorption (CFA) during Creon treatment minus during placebo treatment [Creon minus placebo].

The CFA is a test that is performed by having a patient consume a pre-determined amount of dietary fat and measuring the unabsorbed fat that is excreted in the stool. The CFA, therefore, is a measurement of dietary fat absorption based on stool fat excretion expressed as a percentage of the fat ingested. Healthy infants less than 6 months old can absorb >85% of the fat ingested (i.e., CFA >85%), and healthy adults have CFAs >95%. Exocrine pancreatic insufficiency patients have varying amounts of residual fats resulting in lower than normal CFAs. Treatment may increase CFA to near normal levels (e.g., >85%). In severely affected patients, which is generally defined in the literature as patients with no-treatment CFA <40%, increases of >30% with treatment are generally believed to be clinically meaningful, but clinically meaningful increases in less severely affected patients have not been clearly defined. Overall, however, CFA is a well-established marker for control of steatorrhea, and has been deemed as an acceptable surrogate endpoint by the Agency, as stated in the Guidance. Due to the body of evidence that supports using CFA as an endpoint, it is acceptable that a short-term study be submitted to support efficacy based on the CFA. Although the Applicant submitted Coefficient of Nitrogen Absorption (CNA) results, as well as other markers such as changes in stool weight and frequency, the Division felt that these endpoints have not been described in the literature as a widely accepted markers of efficacy that have been established to correlate with long-term clinical benefits. Therefore these additional endpoints were not agreed upon for inclusion in product labeling based on the results from a short-term study.

Results

A total of 35 patients consented to enroll in the study, of which there were 34 unique patients (1 patient was re-randomized after premature discontinuation from the first cross-over period). Of these 34 unique subjects, 2 were screen failures. Additionally, one patient prematurely discontinued from the study because he had violated the inclusion criteria¹⁵. In the Pivotal study, efficacy was defined as the mean change in CFA (Creon minus placebo) for the full analysis population, i.e., all 31 patients who received ≥ 1 randomized dose who also had CFA assessments during both cross-over treatment periods.

Demographic and baseline characteristics for both treatment sequence groups were similar, with a mean age of 22 years and the majority being Caucasian (>93%) and male (>56%). The study discontinuation rate for each group was 0% in the placebo→Creon sequence group, and 6% (1 in 16) in the Creon→placebo sequence group.

In the full analysis population, the adjusted mean treatment difference between Creon vs. placebo was 39% (95% CI 32, 46), favoring Creon treatment, $p < 0.001$, using ANOVA modeling with treatment, sequence, and cross-over period as fixed effect and patient within sequence as a random effect (table copied electronically from the Statistical Review).

¹⁵ The patient was discontinued from the study because 1 day after taking all Creon treatment during the first cross over treatment sequence, the Investigator found that the patient had violated an exclusion criterion i.e., he had had weight loss $\geq 5\%$ within 3 months prior to enrollment, and that he should not have been enrolled.

Study S245.3.126: Change in CFA (%) for ITT Population			
	Pancrelipase	Placebo	Pancrelipase - Placebo
n	31	31	
Sample Mean (s.d.)	88.6 (6.6)	49.8 (18.3)	
Adjusted Mean (s.e.)	88.6 (2.3)	49.6 (2.3)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			39.0 (32.3, 45.8)
p-value for Adjusted Mean Treatment Difference			<0.001

Source: Table 9 on page 54 of Study S245.3.126 report.

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.

Dr. Castillo highlighted two statistical issues in this submission: 1) one subject was re-randomized at one center after he failed to complete the second half of the first cross-over treatment sequence, and only the data from the re-randomized occurrence was used in the analysis, and 2) one center (Site 23) was suspended by the Applicant because of questionable data quality.¹⁶ To address these statistical issues, the Statistical Reviewer conducted a primary efficacy sensitivity analysis using the second randomization of the subject who was re-randomized and without the two subjects from Site 23. The results did not change the efficacy conclusions of the study.

Subgroup analyses of the primary outcomes were conducted by, gender, age group, and baseline disease severity (analysis by race could not be performed because all patients were Caucasian). For the age and gender subgroup analyses, the observed treatment effects were generally in the same range as the overall effect, although the study size was too small to allow definite conclusion. For the subgroup analysis by baseline disease severity, results showed that severely affected patients (i.e., patients with placebo [no-treatment] CFA <40%) had greater increases in CFA with Creon treatment than the less severely affected patients. This result is consistent with what is known in the literature and observed in other PEP studies.

Conclusions and Recommendations

The Statistical Reviewer concluded that the results reported in the submission supported the conclusion that Creon is efficacious for treatment of EPI in CF patients ages 12 and older, by demonstrating a statistically significant increase in the CFA for the Creon 24,000 capsules, given as 4000 lipase units per gram of fat ingested per day, compared to placebo.

The Clinical Reviewer concluded that the Pivotal Study demonstrated Creon is effective in improving CFA in the treatment of steatorrhea in patients with EPI due to CF in patients ages 12 and older, and that the results were clinically meaningful. The efficacy profiles were similar between genders and across age groups; however, the most severely affected patients (i.e. patients with no-treatment CFA \leq 40%) tend to have the greatest response to treatment, and those patients with higher no-treatment CFA tend to have a lesser response.

The Clinical Reviewer felt that even though the Pivotal Study only enrolled patients down to 12 years of age, it would be appropriate to extrapolate efficacy to patients down to 1 month of age (which is usually the earliest time in life when PEP therapy begins), given 1) efficacy has been demonstrated in the TbMP in children 12 to 18 years of age, 2) there is extensive history of efficacy of PEPs as a class for both adults and children, 3) there is extensive literature that supports the use of CFA as an endpoint in both adults and children, 4) given

¹⁶ A DSI site inspection was completed. See Section 11. Other Relevant Regulatory Issues, DSI Audits.

that the disease characteristics and pathophysiology are similar across age groups and the site of action is local within the lumen of the gastrointestinal tract, children younger than 12 years of age are expected to respond to treatment as children older than 12 years of age and adults, and 5) prior clinical study using the CMP demonstrated similar efficacy in children as young as 1 month of age (see Section 10 Pediatrics for more details). Efficacy could also be extrapolated to patients who suffer EPI from other causes (for example, chronic pancreatitis due to alcoholism or pancreatectomy) given that there is a general consensus that EPI due to any cause has similar clinical findings and should respond similarly to this drug. Thus, the Clinical Reviewer concluded that the information in the application supported approval for the treatment of steatorrhea due to EPI caused by CF and other conditions, and that Creon be indicated for patients of any age, including the youngest pediatric patients because efficacy could be extrapolated to the younger population. He concurred that dosing is to follow the CFF Guidelines, which the Agency has previously concluded to be an appropriate approach based on extensive evidence in the literature.

8. Safety

The reader is referred to the Clinical Review by E. Hausman dated April 30, 2009.

Porcine-derived PEPs have been in clinical use since prior to 1938, and as such there is extensive clinical experience with these products that demonstrate that PEPs are relatively safe, and the adverse event (AE) profile has been well described in the medical literature to include fibrosing colonopathy, hyperuricemia, and allergic reactions to porcine derived products. The clinical benefits of PEP treatment have also been established. For example, evidence in the literature have shown that pediatric patients have better clinical outcomes with PEP administration in growth and development, maintaining weight and pulmonary functions, and have fewer disease complications, rendering a favorable risk/benefit profile. In consideration of the extensive experience with PEPs, the Guidance stated that it is not necessary to conduct long-term safety evaluations; however, a short-term safety evaluation is required.

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 by the Clinical Reviewer. In general, the safety findings in these other 59 studies were similar to clinical findings published in open-source literature. Most AEs were associated with primary disease processes, complications of primary disease processes, or unrelated causes. 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 comparability (i.e. *in vivo* duodenal lipase activity) of TbMP and non-TbMP formulations have not been established, and the two products are not considered interchangeable, a determination of approval relies mainly on clinical data from the Pivotal study supported by extensive evidence in the medical literature, and that labeling will need to clearly delineate the safety information that comes from the placebo-controlled Pivotal Study using the TbMP. Information in the label derived from literature reports on other PEP formulations will be clearly described as such.

The total duration of the Pivotal Study was approximately 2 weeks. Mean duration of exposure to the study drug was approximately 5 days. There were no deaths in the Pivotal Study. Two serious adverse events (SAEs) were reported in a single patient, a 12-year old boy in the Placebo→Creon group who experienced duodenitis and gastritis approximately 2 weeks after his final Creon dose when he was placed back on his prior PEP. The patient received Creon dosing above the CFF recommended maximum dose during the study (i.e., his average daily dose was 4,331 lipase units/gram of fat ingested per day, or 22,908 lipase units/kg of body weight per day, in excess of the Guideline maximum dose of 4,000 lipase units/gram of fat ingested per day, or 10,000 lipase units/kg of body weight per day). Also, his pre-study PEP dose was 7,339 lipase units/kg of body weight per day. Thus, during the study, he received approximately three times his pre-treatment lipase dose. The patient recovered without sequelae. A causal relationship of these events to either treatment could not be ruled out.

One patient dropped out of the study due to weight loss >5% within 3 months prior to enrollment, which violated an exclusion criterion, and the event was not likely related to Creon.

There were two severe AEs in a single patient, who experienced upper abdominal pain during placebo treatment and dizziness during planned phlebotomy during Creon treatment, and both events occurred prior to first Creon study drug exposure, and were unlikely drug related.

No cases of FC were observed, which was expected given the short duration of the study period and the development of FC is unlikely an acute event. Further, since FC is a histopathologic diagnosis, and surveillance with endoscopy with biopsy was not performed as a study procedure, subclinical cases would not have been detected. Therefore the Reviewer concludes that the risk of FC with the TbMP is not refuted by absence of safety findings in the Pivotal Study, and that this known serious risk should be addressed in labeling.

Administration of PEPs is associated with hyperuricemia and hyperuricosuria, due to gastrointestinal absorption of residual porcine purines not eliminated in the product process. There were no clinically meaningful differences in blood uric acid levels during Creon vs. placebo treatment, however, given the short duration of the study period, the potential for hyperuricemia still exist, and risk of hyperuricemia is to be addressed in labeling to warn the risk of hyperuricemia, which could worsen their condition(s) in patients with hyperuricemia, gout, or renal impairment.

Three patients with normal absolute neutrophil counts (ANCs) during screening experienced decreases in neutrophil count with Creon treatment. One of the patients met the laboratory definition of moderate neutropenia, which resolved by the end of the washout period after Creon treatment. The patient was receiving Creon and a macrolide antibiotic. Decreases in ANC after Creon treatment in the other two patients did not meet the clinical definition of absolute neutropenia. Review of the case report forms did not relate these laboratory findings to any clinical manifestations. The Reviewer felt that the clinical significance of these results is unknown, and the small patient population and short duration of the study

limits the ability to draw conclusion; however, a causal relationship by Creon cannot be ruled out and the case of neutropenia should be reflected in the labeling.

Overall, AEs during Creon treatment were similar in types 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 (71%) than Creon (50%) treatment. The most common AEs during Creon treatment were abdominal pain, flatulence, followed by dizziness, headache, cough and nasal congestion. The most common AEs during placebo treatment were abdominal pain, flatulence, and headache. GI-related AEs were more common in the placebo group, which likely reflected lack of efficacy due to placebo treatment.

Conclusions

The Clinical Reviewer concluded that, overall, Creon appears to have an acceptable short-term safety profile, and believes that Creon's long term safety profile is likely comparable to other PEP formulations, which appear to have a favorable overall risk/benefit profile. The Reviewer recommended that the labeling include warnings about FC, hyperuricemia, and allergic reactions, and potential viral exposure from the product source. The Adverse Reactions section of labeling should describe the short-term safety based on the placebo-controlled Pivotal Study, including a description of duodenitis and gastritis, and transient neutropenia as described.

The Reviewer also conveyed during labeling negotiation that postmarketing safety information should include the most serious adverse events that were described in the integrated summary of safety (ISS) and a post-marketing safety report, which include safety information from non-TbMP PEPs (see Section 6.2 Postmarketing Experience). The Reviewer expressed that these serious adverse events are worth mentioning in the labeling because they are not only reported in the ISS, but are also described in the medical literature. They include "FC, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives and pruritus." Additionally, "the most commonly reported adverse events were gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, constipation, and nausea, and skin disorders, including pruritus, urticaria, and rash." He agreed with inclusion of the statement that "the long-term safety profile of these products has been described in the medical literature" in the Postmarketing Experience section.

The Reviewer agreed with PeRC recommendation that the totality of clinical information submitted in the NDA as well as information from the substantial literature base, as summarized in his review, supported the determination that safety may be extrapolated down to children 1 month of age to allow the indication for treatment population to include children less than 12 years of age (see Section 10 Pediatrics). The Reviewer concurred with DTP that long-term follow up for viral transmission should be carried out as a postmarketing requirement.

9. Advisory Committee Meeting

This application was presented to the Antiviral Advisory Committee on December 2, 2008, which included experts from the NIH, the CDC, and the USDA, as well as representatives from industry, academic and patient communities to discuss the risk of viral transmission from this and other porcine-derived PEPs. The closed session held discussions containing proprietary information on manufacturing testing methods for viruses and viral control strategies. In the open session, testing and lot release criteria, and continuing risk identification and mitigation strategies were discussed. Although there has been no documentation of viral transmission to humans, the Committee generally agreed that there is a theoretical (though an exceedingly rare) risk of viral transmission to patients treated with porcine-derived PEPs, including Creon (TbMP). The Committee felt that patients and their physicians should be informed of this risk, but that FDA's warning should not be escalated to a level where the overall risk/benefit profile is skewed towards unfavorable to deter the patients from taking this medically necessary product. The Committee also voted that the Applicant should be required to submit and implement a detailed plan for animal disease surveillance programs, as well as a plan for continued viral risk identification and evaluation in patients taking Creon in the post-marketing clinical setting. The Committee recommended that risk evaluation and mitigation be collaborative, with organizations such as the NIH, CFF, and National Pancreas Foundation. See full transcript for the AC open session at <http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs> for details.

10. Pediatrics

PEPs are not orphan products and therefore are subject to the Pediatric Research Equity Act of 2003 (PREA). The PEP Guidance states that 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), but that *clinical studies may not be needed in each pediatric age group if data from one age group can be extrapolated in another* (with emphasis added). 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. Because solid dosage forms of PEPs cannot be swallowed by young pediatric patients (i.e., generally 6 years of age or younger), under PREA, Applicants must attempt to develop age-appropriate formulations for this patient population.

Consistent with the Guidance, the Division recommended approving Creon (TbMP) without restriction for use in children of all ages based on the following. The medical literature includes publications of studies of PEPs in adults and children. The endpoints of those studies include changes in coefficient of fat absorption and stool frequency. These publications demonstrate PEPs have efficacy, as measured by coefficient of fat absorption, in both adults and children. While it is unethical to conduct a placebo-controlled trial of the duration required to document change in growth, (indirect) evidence of the impact of PEPs on growth in children can be derived from population studies that show children who are diagnosed early secondary to newborn screening programs and, as a result, receive early

aggressive management of nutrition and pulmonary care demonstrate better growth in early childhood.^{17,18} The medical literature is also replete with information on the safety profile of PEPs in children, since PEPs are part of standard management of children with cystic fibrosis with exocrine pancreatic insufficiency and fat malabsorption. Given that the disease characteristics and pathophysiology are similar across age groups and the site of action is local within the lumen of the gastrointestinal tract, children younger than 12 years of age are expected to respond to treatment as children older than 12 years of age and adults. Therefore, DGP in consultation with the Pediatric Review Committee (PeRC) deem it appropriate to extrapolate both efficacy and safety data for the TbMP, from children ≥ 12 years of age to children ≤ 12 years. The DGP met with the PeRC twice to discuss this issue, on November 12, 2008 and on March 18, 2009. Statements about the approvability of the TbMP in pediatric age groups in the FDA's Briefing Document and presentations for the December 2, 2008 Advisory Committee are superseded by the conclusions reached with the PeRC at the meeting on March 18, 2009. At the March 2009 meeting the Division and PeRC reached the conclusion that the TbMP indication would not need to be limited to the age group included in the studies conducted with the TbMP. That is, the indication should be extended to all pediatric patients.

The Division and PeRC also agreed that due to the low incidence/diagnosis of EPI in pediatric patients below age 1 month, and necessary studies are impossible or highly impractical in this population, PREA requirements could be waived for patients who are \leq age 1 month.¹⁹

Finally, since Creon will almost certainly continue to be used by pediatric patients as young as 1 month of age, a formulation of Creon suitable for administration to pediatric patients unable to swallow capsules will need to be developed in accordance with PREA regulations. FDA is concerned that opening capsules and sprinkling pellets and estimating the dose may pose some risk of lipase overexposure to the youngest patients and increase the risk of FC in the patients who are most at risk of experiencing this complication. In her Pediatric Consult review, the Reviewer (F. Collins) cites the example of use by infants up to 12 months, for whom the CFF Guidelines recommend PEP dosing of 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding. If Creon capsules (6000 lipase units) were used in this population, the parent and/or caregiver would have to approximate the 1/3 to 2/3 of the capsule contents to achieve the recommended dose. Such an approximation likely would be difficult to do. On the other hand, if a 1-month old girl weighing 4 kg (50th percentile weight for age) were given the entire 6000 lipase units, this would equate to 1,500 lipase units/kg which is less than the generally recommended maximum dose of 2,500 lipase units/kg per meal. However, 6000 lipase units per meal for an infant eating 8 – 12 times a day would

¹⁷ Siret D, Bretaudeau G, et al. Comparing the Clinical Evolution of Cystic Fibrosis Screened Neonatally to that of Cystic Fibrosis Diagnosed from Clinical Symptoms: A 10-Year Retrospective Study in a French Region (Brittany). *Pediatric Pulmonology* 2003; 35:342-349.

¹⁸ Farrell PM, Kosorok MR, et al. Nutritional Benefits of Neonatal Screening for Cystic Fibrosis. *NEJM*.1997, Vol 337, No 14: 963-969.

¹⁹ The PeRC concurred with DGP's decision to waive studies in the youngest pediatric age group (newborns up to 1 month of age) because diagnosis of CF generally is not made until after 1 month of age. Even if an infant is part of a newborn screening program, test results and diagnostic work-up are often not complete until nearly 1 month of age. In addition, the small number of patients diagnosed in this age category and the geographic dispersal would make conduct of a study in this age group highly impracticable.

result in 48,000 – 72,000 lipase units per day (12,000 – 18,000 lipase units/kg per day for a 4 kg infant). This would exceed the current recommendation of 10,000 lipase units/kg per day. This Reviewer agrees that given that PEPs are a medically necessary product, the TbMP should not be withheld at this time from the youngest patients. However, the Applicant will need to (under PREA) develop an age appropriate formulation for children whose weight dictates a lower capsule strength than is currently available for the TbMP. Pediatric dosing is to follow the CFF Guidelines.

11. Other Relevant Regulatory Issues

Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Creon is not systemically absorbed.

Division of Scientific Investigations (DSI) audits

Three clinical sites were inspected: Site #10, University of Iowa Hospital and Clinics; Site #25, University of Cincinnati; and, Site #23, Long Beach Medical Center. The first two sites were selected for inspection due to having a relatively large number of study subjects. Site #23 was selected because of data quality issues that were uncovered during the review. The field inspector (K. Malek) found that data from Sites #10 and 25 are reliable. However, data from Site #23 (6 patients were screened, but only 2 subjects were randomized and completed the study) do not appear accept in support of the indication, as review of the site revealed protocol deviations that impact the primary efficacy endpoint. As previously noted, the Statistical Reviewer conducted a sensitivity analysis using the ITT population without the 2 subjects from Site #23, where the data quality was in question, and the analysis gave similar results to the ITT analysis.

Eurand's Citizen Petition

On February 6, 2009, Eurand Pharmaceuticals, Inc. petitioned the FDA to address their concerns regarding the trade name, packaging, trade dress, sales, marketing and labeling for the TbMP Creon. The Division does not find that it is a threat to public safety to approve the TbMP at this time with the trade name Creon. Please see FDA's Response to the Citizen Petition FDA-2009-0059 for a detailed discussion.

Drug Shortage

The Applicant informed the Agency in February 2009 regarding the potential of a drug shortage related to Creon. The events leading this shortage are related to other PEP manufacturers that have failed to comply with FDA's October 2007 FR Notice requirement, and the exit of these products from the market due to voluntary recall at a wholesaler level. The Applicant also stated that there are concerns about obtaining sufficient quantity of APL raw material from their supplier, Scientific Protein Labs (SPL) in the event of increased demand. A potential drug shortage could start in Q2 of 2009. Discussions are ongoing between with the Agency and the Applicant regarding management of the public health needs in the setting of a potential drug shortage.

Other Clinical Studies Planned for the TbMP

The TbMP was submitted for review under NDA 20-725. It is also currently under investigation under IND 47,546. Three planned or ongoing clinical trials are summarized below:

- Study S245.3.127 is evaluating TbMP in children with CF-related EPI ages 7 through 11 years. The Applicant notified the Division that this study has completed and the final study report will be submitted to the NDA in June 2009.
- Study S245.3.128 will evaluate TbMP children with CF-related EPI ages 1 month through 6 years. The protocol has been submitted and reviewed. Enrollment is

expected to begin in summer of 2009 and the final study report will be submitted in July 2010.

- Study 245.3.124 is evaluating TbMP in adult patients with EPI due to chronic pancreatitis or pancreatectomy and the final study report will be submitted on September 20, 2009, as a PMC.

The “Swine Flu” Outbreak, April 2009

The Centers for Disease Control and Prevention (CDC) reports a swine influenza A (H1N1) outbreak at the time of this writing. Cases have been reported in the US and internationally. The CDC states on its website that “cooking pork to an internal temperature of 160°F kills the swine flu virus as it does other bacteria and viruses.”

Influenza A virus is an enveloped RNA virus. DGP has conferred with DTP that the risk of transmission of the Swine Flu to patients by the TbMP is negligible. The probability of natural presence of influenza virus in the raw material is low due to tissue tropism, as pancreatic tissue is not a target site for swine influenza A virus. A secondary contamination of pancreatic tissue with bronchial or nasal fluids or with lung tissue is also of low probability, considering the hygienic controls implemented in the raw material handling, as described in the Applicant’s submission. Even if a secondary contamination of raw material with lung tissue were to accidentally happen, the manufacturing process is able to eliminate this level of viral load because during the manufacturing process, the DS ^{(b) (4)}

which have been shown to effectively inactivate influenza A-like viruses. Finally, oral ingestion of even a contaminated product is unlikely to produce an infection because the H1N1 virus must be transmitted by an inhalational route. In summary the Review Team does not feel that the current swine flu outbreak impedes the approvability of the TbMP at this time.

12. Labeling

Proprietary name

The Division of Medication Error Prevention and Analysis (DMEPA) concluded the proprietary name of “Creon” was acceptable. Please see DMEPA Consult (dated March 27, 2009) by D. Hamilton-Stokes, which documents the extensive review history regarding the acceptability of the TbMP trade name.

DMEPA agreed that the differences in animal source and extraction processing of the API, and in the excipients, though sufficient to render the two products not comparable and therefore not interchangeable, do not represent significant differences enough to necessitate a change in the proprietary name.

DMEPA notes that the TbMP labels and labeling have been revised to accurately reflect the USP units for all three enzymes of the active ingredient, and to correctly reflect the amount of USP units contained in each capsule. DEMP A also notes that several mechanisms have been put in place to mitigate the potential for product confusion. The labeling and Risk Evaluation and Mitigation Strategy (REMS) for the TbMP, which includes a Medication Guide, will inform patients regarding the different stability, dosing instruction, and labeled

dosage strengths. The Creon TbMP packaging and trade dress already contain visual element features that would differentiate the TbMP from the CMP. A comprehensive transition plan has been proposed to minimize the time that the TbMP and the CMP will co-exist in the market. As part of the transition plan, the Applicant will disseminate a Dear Health Care Provider Letter and Dear Pharmacist Letter at TbMP launch that will inform these professionals regarding the transition between products, including important differences between the two products and the fact that they are not interchangeable. They will also inform them that the elimination of mineral oil from the TbMP may result in changes in fat soluble vitamin levels. These educational letters will be supplemented by sales representative training and field activity. In these considerations DMEPA supports the denial of the Citizen Petition to require the Applicant to use a new proprietary name to market and sell their TbMP.

Division of Drug Marketing, Advertising, and Communications (DDMAC) comments
DDMAC finds the proprietary name acceptable from a promotional perspective.

Patient labeling/Medication Guide

The Patient Labeling and Education Team at the Division of Risk Management concurred with DGP regarding the need for a Medication Guide and Risk Evaluation and Mitigation Strategy (REMS)—see Memo by S. Mills. DRISK concurred that it is important for patients to receive information about proper dosing of pancrelipase products in order to mitigate the risk of FC. Careful dosing and avoidance of self-titration of Creon and other pancrelipase products make patient labeling necessary to patients' safe and effective use of these products. The Reviewer also concurred with class labeling for pancrelipase products regarding the risk of FC and the potential risk of viral transmission. DRISK believes that Creon and other pancrelipase products meet two of three criteria under 21 CFR 208.1 (c):

- The drug product is one for which patient labeling could help prevent serious adverse effects.
- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Initially, the recommended components of the REMS included a Medication Guide, Communication Plan (a one-time Dear Health Care Professional Letter sent out at product launch), and Timetable for Submission of Assessments of the REMS. However, the Applicant expressed that having the Letters as being part of the REMS may convey an undue level of high risk to the public. The Division agreed that the Dear Health Care Professional Letter and the Dear Pharmacist Letter could be disseminated outside of the REMS. Please see the Medication Guide, and the communication Letters for final language.

Selected highlights of labeling issues:²⁰

- Indication should read: “CREON Capsules is a pancrelipase which is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.”
- Dosage should include a statement that Creon is not interchangeable with any other pancrelipase product.
- Dosage should follow the CFF Guidelines, which provides regimens for infants (up to 12 months), children older than 12 months and younger than 4 years, and children 4 years older and adults. Limitations on dosing in order to minimize the risk FC should be included. Contents of the capsule should not be mixed directly into formula or breast milk, as this might disrupt its dissolution integrity (in a mixed-food environment where the pH is greater than 4).
- The Applicant initially proposed four dosing regimens for different patient populations (i.e., those with CF, with CP, with pancreatectomy, or due to other conditions) with EPI. The Division felt, however, that there is insufficient evidence in the literature (or any clinical data in the TbMP) to support specific dosing guidelines for these other conditions. The only guideline that has been supported in the literature is the CFF Guideline, and therefore it should be used for all EPI patients.
- Regarding Table 1 of the label, in this case where some adverse events occurred at a higher incidence in the placebo arm (likely reflecting a lack of efficacy due to no treatment) than the Creon arm, it is allowable to label the events as “adverse events,” as opposed to “adverse reactions.” Labeling of “adverse events” vs. “adverse reactions” is consistent with standards set in Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products -- Content and Format, January 2006.
- Pediatric Use should describe that the Pivotal Study included patients who are ≥ 12 years, and not imply that younger children have been studied with the TbMP. It should be mentioned that the safety and efficacy of PEPs with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with EPI due to CF have been described in the medical literature and through clinical experience. Dosing of pediatric patients should be in accordance with recommended CFF Guidelines.
- The product label throughout should not refer to the CMP or to specific data from studies of CMP.
- The Clinical Studies section should describe the efficacy results from the Pivotal Study. Subgroup analysis to mention that patients with a lower no-treatment (placebo) CFA values showed greater improvement in CFA with treatment, than

²⁰ This Reviewer served as the Acting Team Leader for the Creon project up to March 20, 2009; negotiations with the Applicant and finalizing the approval process thereafter were conducted under the team leadership of Dr. A. Pariser, and DGP directorship of Dr. D. Griebel.

those with higher no-treatment (placebo) CFA values should be included. There were no differences in responses to Creon by age or gender.

- References could be included for this class of drugs that rely on evidence in medical literature for approval, and in fact contains dosing guidelines that are published in the medical literature.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

All the primary review disciplines recommended the product for approval. This Reviewer concurs with the approval recommendation.

Risk Benefit Assessment

The risk and benefit characteristics appear similar to those of already marketed PEPs for treatment of EPI. The product has a favorable risk/benefit profile.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

A REMS is recommended, with the following language for the Approval Letter:

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Creon (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweighs the risk of fibrosing colonopathy with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients. The REMS, once approved, will create enforceable obligations.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Creon (pancrelipase) Delayed-Release Capsules poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Creon (pancrelipase) Delayed-Release Capsules. FDA has determined that Creon (pancrelipase) Delayed-Release Capsules is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Creon (pancrelipase) Delayed-Release Capsules. In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Creon (pancrelipase) Delayed-Release Capsules.

Your proposed REMS, submitted on April 17, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the Timetable for Submission of Assessments of the REMS included in your April 17, 2009 submission.

Your REMS assessment plan should include an evaluation of:

- a. Patients' understanding of the serious risks of Creon (pancrelipase) Delayed-Release Capsules
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Recommendation for Postmarketing Required Pediatric Studies

Development of an age appropriate formulation under PREA is recommended, with the following language for the Approval Letter:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

1. Deferred requirement for development of an age appropriate formulation for Creon (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by December 31, 2010.

We are waiving the pediatric study requirement for ages 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, so there would not be enough eligible patients in this age range to study.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

Recommendation for other Postmarketing Study Requirements (PMRs)

PMR studies are recommended, with the following language for the Approval Letter:

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

2. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Creon (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 20, 2010
Study Completion Date:	by January 1, 2021
Final Report Submission:	by June 20, 2021

3. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Creon (pancrelipase) Delayed-Release Capsules.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 20, 2010
Study Completion Date:	by January 1, 2021
Final Report Submission:	by June 20, 2021

Recommendation for other Postmarketing Study Commitments (PMCs)

PMC studies are recommended, with the following language for the Approval letter:

We remind you of your postmarketing commitments in your submissions dated March 6, 2009 and April 17, 2009. These commitments are listed below.

4. Solvay commits to complete Study S245.3.124, a multi-center, randomized, double-blind, placebo-controlled trial of the safety and effectiveness of Creon (pancrelipase) Delayed-Release Capsules in patients 18 years and older with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. The study will have an open-label 6-month extension.

Final Report Submission: by September 20, 2009

5. Solvay commits to perform routine monitoring of the enveloped viral load entering the manufacturing process. The control strategy will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with action limits and specifications.

Final Protocol Submission: by October 20, 2009

Final Report Submission: by October 20, 2010

6. Solvay commits to continue developing sensitive qPCR assays that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded. The revised assay and assay validation data, together with new action limits, will be submitted to the Agency.

Final Report Submission: by October 20, 2009

7. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the drug substance. The proposed methods, including relevant method validation, will be submitted to the Agency.

Final Report Submission: by October 20, 2010

8. Solvay commits to assess the risk to product quality associated with porcine hokovirus, and submit a control strategy for mitigating this risk to product quality.

Final Report Submission: by October 20, 2009

9. Solvay commits to revise the acceptance criteria for the viral infectivity tests for swine vesicular disease virus (SVDV), encephalomyocarditis virus (EMCV) and porcine rotavirus (Rota) to “none detected.”

Final Report Submission: by July 1, 2009

10. Solvay commits to provide detailed plans for its animal disease surveillance program and continued risk assessment evaluation for source animals. The proposed plans will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these plans will be implemented.

Final Report Submission: by October 20, 2009

11. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites.

Final Report Submission: by October 20, 2009

12. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues.

Final Report Submission: by October 20, 2009

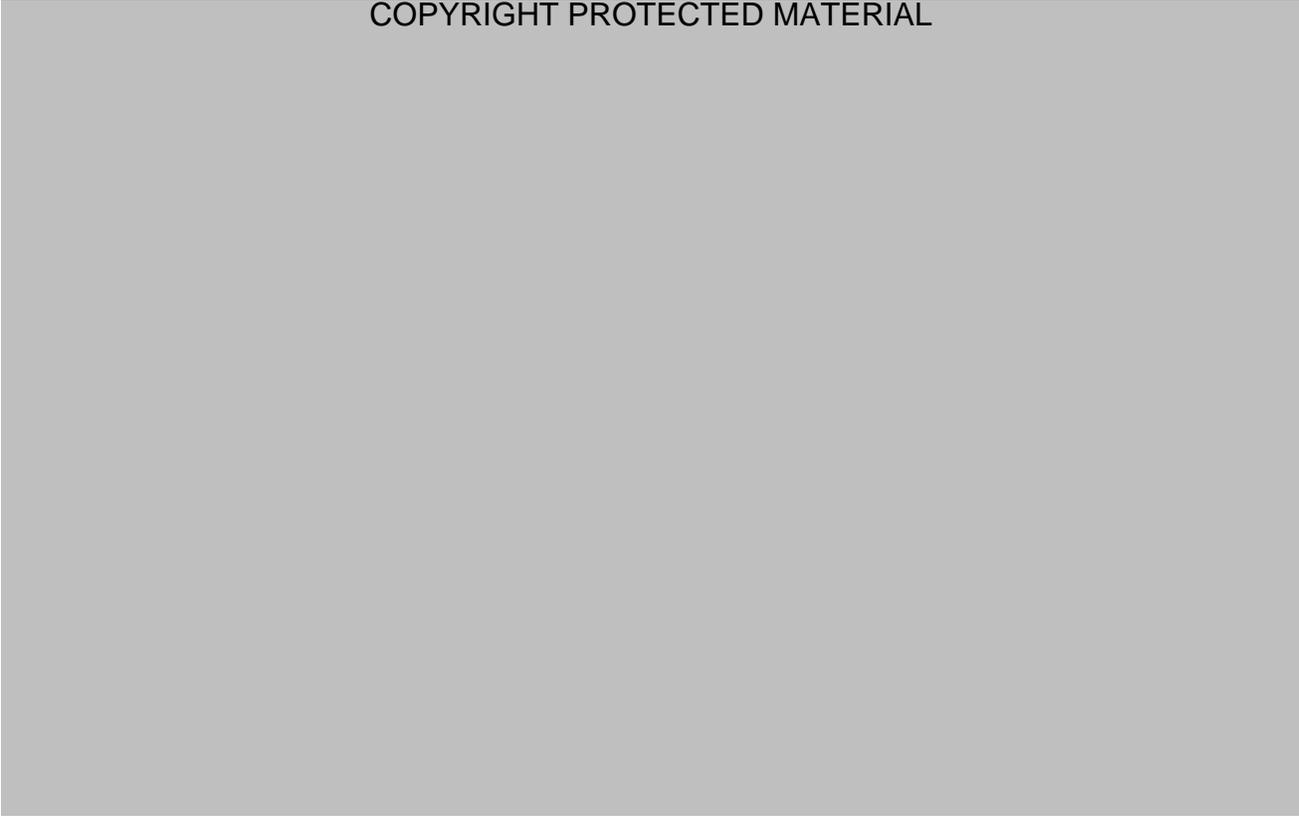
Recommended Comments to Applicant

None.

14. Appendix

The CFF Dosing Guidelines are derived from the paper by Borowitz et al, 1995:

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²¹ Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127:681-684.

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/s/

Joanna Ku
4/30/2009 05:47:01 PM
MEDICAL OFFICER

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