CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 12, 2010
From	Anil Rajpal, MD, Acting Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-523
Applicant	Johnson and Johnson Pharmaceutical Research and Development, L.L.C.
Date of Submission	June 23, 2009; Received June 23, 2009
PDUFA Goal Date	April 23, 2010
Proprietary Name / Established (USAN) names	Pancreaze® / pancrelipase
Dosage forms / Strength	Pancreaze® (pancrelipase) delayed release-capsules for oral administration, in USP units ▪ Pancreaze 4,200 lipase/10,000 protease/17,500 amylase ▪ Pancreaze 10,500 lipase/25,000 protease/43,750 amylase ▪ Pancreaze 16,800 lipase/40,000 protease/70,000 amylase ▪ Pancreaze 21,000 lipase/37,000 protease/61,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Approval under 21 CFR 314

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1. Introduction

This submission, received April 23, 2009, is the initial New Drug Application (NDA) for Pancreaze (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP). Pancreaze is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

2. Background

2.1 Clinical Background

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. The most common cause of EPI in children is Cystic Fibrosis (CF); the most common cause of EPI in adults is chronic pancreatitis (CP). There are many other causes, such as pancreatectomy.

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause. Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

Fibrosing colonopathy (FC) is an important safety concern regarding PEP use. Although the etiology of FC is not known with certainty, FC has been associated with high dose PEP exposure. Consensus guidelines have been established by the CFF in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[1,2,3] (See also Section 8 and Appendix 1.)

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

Approved PEPs: Only three PEPs have been approved under NDA to date:

(1) Cotazym (NDA 20-580): approved in 1996; not currently marketed

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

[2] Borowitz DS, Grand RJ, Durie PR, et al., Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127:681-684.

[3] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

(2) Creon (NDA 20-725): approved April 30, 2009
(3) Zenpep (NDA 22-210): approved August 27, 2009

Thus, there are only two approved PEPs, Creon and Zenpep, that are currently commercially available in the US.

Other PEPs: Other than Creon, PEPs currently available have not undergone formal evaluation under NDAs for efficacy or safety. PEPs have been available since prior to the Federal Food, Drug, and Cosmetic Act of 1938; most PEPs have been available since before Drug Efficacy Study Implementation (DESI; pre-1962).

Federal Register Notices: Over the past many years, the FDA has published a number of notices in the Federal Register (FR) with the aim of requiring all marketed PEPs to have undergone the NDA application and review process. This is largely to address variations in formulation, dosage, and manufacturing processes, both between different PEPs and within individual PEP brands. Recent FR notices for PEPs are summarized in the table below.

Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products

Year	Federal Register Notices
April 1995	Notice of Final Rule: All PEPs must obtain FDA approval under NDA in order to remain on the market.
April 2004	Notice of Requirement for NDA Approval: All PEPs must obtain NDA approval within the next four years (deadline April 28, 2008)
October 2007	Notice of Extension: FDA would use enforcement discretion for the PEPs. In order to continue marketing their products, manufacturers must have: ▪ open IND by April 28, 2008, ▪ NDA submitted by April 28, 2009, and ▪ approved NDA by April 28, 2010.

PEP Guidance: It should also be noted that the draft PEP guidance was published in 2004, and the final PEP Guidance was published in 2006 (Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs).

REMS for Creon and Zenpep: A Risk Evaluation and Mitigation System (REMS) was implemented for Creon and for Zenpep for two reasons:

(1) Risk of Fibrosing Colonopathy: To address the concern that the risk of FC may be increased with high dose exposure to PEPs, a Medication Guide that informs patients of the risk of FC is part of the REMS for Creon and for Zenpep. (See also Section 2.1 and Appendix 1.)
(2) Risk of Transmission of Viral Disease to Patients: There is a concern that because Creon, Zenpep, and other PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude

patients from receiving the drug.[4,5] To address the concern about the theoretical risk of viral transmission, a Medication Guide that informs patients of the theoretical risk of viral transmission is part of the REMS for Creon and for Zenpep. (See also Section 3.1.1)

2.2.2 Regulatory History of Pancreaze

Pancreaze has been marketed in the United States since 1988 under the name "Pancrease MT." The manufacturing process and formulation of the product have not significantly changed since that time. The current Commercially Marketed Product (CMP) and the To be Marketed Product (TbMP) are believed to be the same formulation.

The table below summarizes the regulatory activity of Pancreaze for EPI.

Table 2. Pertinent Regulatory History of Pancreaze

Date	Action
August 2006	Meeting with the Division to discuss CMC requirements for NDA submission
January 2008	End of Phase 2 Meeting
May 2008	Original IND submission (included protocol for pivotal trial PNCRLPCYS3001)*
December 2008	Meeting with the Division to discuss NDA submission requirements
April 2009	Fast Track Designation / Rolling Review granted
June 2009	NDA 22-523 submitted for Pancreaze

* IND 74893

At the End of Phase 2 meeting, the Sponsor proposed a randomized withdrawal study design for the pivotal study based on a publication by Stern et al.[6,7] Agreement was reached with the Division on the proposed study design at that meeting.[7] The study design was also agreed upon in the clinical review of the pivotal study protocol.[8] It should be noted that the design of the Pancreaze pivotal study differed from that of the Creon and Zenpep pivotal studies which were each cross-over studies.

See the Clinical Review by Ali Niak for details of the Pancreaze regulatory history.

2.3 Current Submission

The NDA submission was received on July 23, 2009. It was classified as a ten-month submission with a PDUFA deadline of April 23, 2010.

No Advisory Committee meeting was convened to discuss this application.

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[4] Antiviral Drugs Advisory Committee (December 2, 2008);
<http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiviralDrugs>
[5] Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.
[6] Stern et al.,, A Comparison of the Efficacy and Tolerance of Pancrelipase and Placebo in the Treatment of Steatorrhea in Cystic Fibrosis Patients With Clinical Exocrine Pancreatic Insufficiency, Am J Gastroenterol 2000;95(8):1932-8.
[7] End of Phase 2 Meeting Minutes dated January 25, 2008 for meeting January 16, 2008 (IND 74,893)
[8] Medical Officer Review of protocol PNCRLPCYS3001 by Joanna Ku (IND 74,893)

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

(1) Clinical Review by Ali Niak, dated April 12, 2010
(2) Statistics Review by Shahla Farr, dated March 1, 2010
(3) CMC Reviews from Division of Therapeutic Proteins (DTP):
    (a) CMC Review of Drug Substance (DMF 7090) by Howard Anderson, dated August 18, 2009
    (b) CMC Review of Drug Product by Howard Anderson (NDA 22-523), dated April 12, 2010
(4) Microbiology Review by Bryan Riley, dated November 23, 2009
(5) ONDQA Biopharmaceutics Review by Tien-Mien Chen, dated March 10, 2010
(6) Pharmacology/Toxicology Review by Ke Zhang, dated April 2, 2010
(7) Clinical Pharmacology Review by Lanyan Fang dated March 15, 2010
(8) DMEPA Reviews:
    (a) DMEPA Proprietary Name Review by Anne Crandall dated January 25, 2010
    (b) DMEPA Label and Labeling Review by Anne Crandall dated February 18, 2010
(9) DSI Review by Khairy Malek, dated March 15, 2010
(10) DRISK Review by Steve Morin, dated March 24, 2010
(11) DDMAC Review by Shefali Doshi, dated March 3, 2010

The reviews should be consulted for more specific details of the application.

3. CMC

The reader is referred to the CMC Review of Drug Substance by Howard Anderson dated August 18, 2009, the CMC Review of Drug Product by Howard Anderson dated April 12, 2010, and the Microbiology Review by Bryan Riley dated November 23, 2009 for complete information.

Overview of Drug Substance (DS): The DS is manufactured by Nordmark, the Drug Master File (DMF) holder (DMF #7090); the DMF has been cross referenced by Johnson & Johnson in NDA 22-523. DS is derived from porcine pancreas glands harvested from pigs raised for consumption as food. The glands then undergo (b) (4) (b) (4) (b) (4) The resulting pancrelipase DS is to be used for manufacture of DP. It should be noted that Zenpep (NDA 22-210; Eurand) uses the same DS as Pancreaze.

Overview of Viral Issues: Given the source of the material, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known to be present in swine include enveloped, non-enveloped, and emerging viruses listed and considered in detail in the virology review. Three viral inactivation steps are involved in the DS manufacturing process, including (b) (4)

steps. To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

Overview of Drug Product (DP): The DP is manufactured by Nordmark; it should be noted that all pertinent information related to the DP has been submitted to NDA 22-523 rather than the DMF. The DP manufacturing process entails: (b) (4) (b) (4) (b) (4). Pancreaze is presented in four strengths, based on lipase activity (4,200; 10,500, 16,800; and 21,000 USP units).

Dosage Strength Formulations: The four dosage strength formulations are MT 4.2, MT 10.5, MT 16.8, and MT 21 capsules containing 4,200, 10,500, 16,800, and 21,000 USP units (U) lipase respectively. MT 4.2, MT 10.5, and MT 16.8 each have the same ratios of lipase:amylase and lipase:protease; MT 21 has a higher ratio of lipase:amylase and lipase:protease than MT 4.2, MT 10.5, or MT 16.8. The microtablet size of each of the four dosage strength formulations is 2 mm. Stability studies with microtablets mixed in acidic soft food (such as applesauce or sweet potato) were conducted to support the use of such foods to administer the microtablets (see Section 5 Clinical Pharmacology).

Packaging: The capsules are packaged in amber glass bottles. Only bottles for the lowest strength capsule (4,200 USP lipase units) contain a desiccant package.

3.1 Issues

Deficiencies identified in the Drug Substance Review, the Drug Product Review, and the Microbiology Review are provided below:

3.1.1 DS Viral Issues

The DS reviewer noted that deficiencies exist, but do not preclude approval of the application since these can be addressed as postmarketing commitments (PMC's). (See Drug Substance Review by Howard Anderson for complete information.)

DS viral deficiency items to be communicated to Nordmark (taken from Dr. Anderson's review) are provided below. (See also Section 13.1.)

1. Develop and validate an infectious assay for PCV1. (Final Report Submission by January 31, 2011)

2. Establish lot release specifications for PCV1 for the drug substance. (Final Report Submission by July 31, 2011)

3. Perform additional monitoring of viral load entering the manufacturing process. The control program will include monitoring for human pathogenic viruses by qPCR. An appropriate control strategy will then be implemented. (Final Report Submission by July 31, 2011)

4. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Revise the assays, and submit assay validation data, together with acceptance criteria. (Final Report Submission by January 31, 2011)

It should be noted that each of the above four postmarketing commitments were also communicated to Eurand (NDA 22-210) in the Approval Letter for Zenpep.

The DS Reviewer noted that although the NDA for Pancreaze is an original submission, there is an extensive regulatory history of the drug substance used to produce Pancreaze because the Zenpep NDA 22-210 (submitted by Eurand a different manufacturer) approved by FDA in August 2009, also uses the same drug substance. A number of viral DS issues were resolved between the first and second submissions of the Zenpep NDA.

- First cycle of Zenpep NDA Review: Viral DS issues in the first cycle were related to the following: (1) risk mitigation for adventitious agents; (2) viral inactivation studies; (3) validation of PCR tests; (4) validation of viral infectivity assays; and (5) specifications for adventitious agents. (See final wording of Items #1 to #5 in letter to Nordmark in Appendix 2.)
- Second cycle of Zenpep NDA Review: Viral DS issues identified in the first cycle were resolved in the second cycle. (See discussion of viral DS issues in Appendix 3.)

[A more detailed discussion of the viral DS issues from the first and second cycle of the Zenpep NDA Review can be found in the CDTL Review of Zenpep (NDA 22-210) dated August 21, 2009.]

3.1.2 DS Non-Viral Issues

There are no current DS non-viral deficiency items.

The DS Reviewer noted that although the NDA for Pancreaze is an original submission, there is an extensive regulatory history of the drug substance used to produce Pancreaze because the Zenpep NDA 22-210 (submitted by Eurand a different manufacturer) approved by FDA in August 2009, also uses the same drug substance. A number of non-viral DS issues were resolved between the first and second submissions of the Zenpep NDA.

- First cycle of Zenpep NDA Review: Deficiency items for non-viral DS issues that were sent to Nordmark were related to: (6) USP lipase, amylase, and protease reference standards; (7) specification for total starting gland weight; (8) plans to re-examine the production process; (9) rejected batches may not be reworked or reprocessed; (10) testing and limits for simethicone levels; (11) release specifications; (12) HPLC assay validation; (13) specification for water content for release testing: (14) colipase specification for DS release; (15) demonstration of predicted lipase activity; (16) olive oil qualification; (17)

DS label; and (18) storage conditions and expiration date. (See final wording of Items #6 to #18 in letter to Nordmark in Appendix 4.)

- Second cycle of Zenpep NDA Review: Non-viral DS issues identified in the first cycle were resolved in the second cycle. (See discussion of non-viral DS issues in Appendix 5.)

[A more detailed discussion of the non-viral DS issues from the first and second cycle of the Zenpep NDA Review can be found in the CDTL Review of Zenpep (NDA 22-210), dated August 21, 2009.]

3.1.3 DP Issues

The DP reviewer noted that some deficiencies exist, but these do not preclude approval of the application since these can be addressed as PMC's. (See Drug Product Review by Howard Anderson for complete information.)

DP deficiency items to be communicated to Johnson & Johnson (taken from Dr. Anderson's review) are provided below. (See also Section 13.1.)

1. Initiate and complete the proposed studies (Protocol #s 04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use. (Final Report Submission by September 30, 2011)

2. Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the Pancreaze manufacturing process. After 50 lots of low-potency microtablets and 25 lots of high-potency microtablets are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability. (Final Report Submission by March 31, 2013)

The DP Reviewer notes that the product quality standard for Pancreaze is equivalent to or exceeds that of the Creon and Zenpep products. The DP Reviewer also noted that the Pancreaze drug product production involves a (b) (4) step that is not present in the other two products; the DP Reviewer points out that the (b) (4) offers an additional viral and microbial reduction or inactivation step that will minimize contamination of the Pancreaze product with these agents.

The majority of deficiencies identified during the review cycle were adequately addressed by information requests during the primary review, and thus do not preclude approval of the application; the remaining pending issues can be addressed as post-marketing commitments (PMCs).

Key information request items and the Applicant's response to each of the items are summarized below:

(1) In-Process Friability Testing: Justification for not conducting in-process friability testing (used to ensure physical integrity of the product). The Applicant adequately responded that a friability specification ((b) (4) USP) will be implemented and the NDA has been updated to include this specification.

(2) Simethicone: Measurement and establishment of acceptance criteria for the process related impurity simethicone. The Applicant indicated that simethicone emulsion is

not a process related impurity but is actually an excipient used in the (b) (4) process, that it is classified as GRAS, is listed on the FDA's inactive ingredients database, and that the levels of maximal exposure to simethicone emulsion are estimated to be (b) (4) mg/kg (b) (4)). The Applicant's response was deemed to be adequate.

(3) Process Validation Protocol: Request for the process validation protocol and any data available for the validation studies to date. The Applicant provided validation protocols and validation reports for the 10.5, 16.8, and 21 capsules to demonstrate control and consistency of the manufacturing process; thus, the Applicant's response was deemed to be adequate. Although the validation reports for the 4.2 capsules are not yet available, the validation protocol for the encapsulation of the 4.2 MT was provided and the validation strategy was identical to that of the other strengths. The DP Reviewer noted that there is no concern with Nordmark's ability to complete the 4.2 encapsulation studies in the near future given the company's past performance. Thus, all concerns regarding process validation have been adequately addressed.

(4) Stability Studies: Information regarding stability of the product under conditions of use by patients. The Applicant has proposed two studies (Protocol #s 04020298 & 04020299) to evaluate the stability of Pancreaze under conditions of use. One study (b) (4) (b) (4) The DP reviewer recommends that initiation and completion of the two proposed studies be addressed as a PMC.

(5) Acceptance Criteria: Amylase and protease assay measurements were provided for different lots. The DP reviewer noted that there is not enough data to establish acceptance criteria that accurately reflect manufacturing history and capability, and recommends that acceptance criteria for the protease and amylase assays be re-evaluated after more experience is gained with the Pancreaze manufacturing process. The DP reviewer further noted that this same deficiency was identified with Zenpep and was addressed as a postmarketing commitment. The DP reviewer recommends that this issue be addressed as a PMC.

3.1.4 Microbiology Issues

The Microbiology reviewer recommends an Approval action based on a satisfactory product quality microbiology review of the information submitted. The reviewer noted that the product was non-sterile, but had acceptable microbial limits release specifications for total bacteria, yeasts and molds. Salmonella and E. coli species are absent. The Microbiology Reviewer did not recommend any comments relating to the microbiology information be communicated to the Applicant.

3.2 Recommendation

An Approval Action is the overall recommendation by CMC.

The DP Review states the following: "The data submitted in this application support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. The conditions used in manufacturing have been validated, and a consistent product is produced by the process. It is recommended that this product be approved for human use (under conditions specified in the package insert)."

The DP Review also notes the following: "Although some lots of pancrelipase have been shown to contain infectious porcine parvovirus (PPV), the risk that PPV can cross species and transmit diseases to humans is minimal, and is outweighed by the clinical benefit provided by pancrelipase."

The DP Review notes that there are deficiencies identified in the NDA and in the DMF but these do not preclude approval of this application since these can be addressed as PMC's. The PMC's concern improving viral detection assays and surveillance strategies during manufacturing of the drug substance, evaluating stability of the drug product under conditions of use, and tightening acceptance criteria for the drug product amylase and protease potency assays. (See Section 13.6 Postmarketing Commitments of this review.)

4. Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Ke Zhang dated April 2, 2010, for complete information.

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance[9], given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Pancreaze clinical development program. However, toxicology studies are needed if the excipients in the Pancreaze DP are not classified as GRAS, and the toxicology program for the excipients should supply data from long-term studies in both rodent and non-rodent mammalian species, plus standard reproductive toxicity and genotoxicity information. Consistent with the Guidance, the Applicant did not conduct any nonclinical studies with Pancreaze in support of this NDA, but did provide published information on the excipients in the formulation studied in the clinical trials of Pancreaze.

Dr. Zhang notes that although the sponsor provided toxicity studies and embryo-fetal developmental studies of pancrelipase, it is uncertain whether the drug substance used in these studies is comparable to the drug substance in Pancreaze.

[9] 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.

Johnson & Johnson provided a comprehensive summary of the toxicology data available for each excipient used in the formulation of Pancreaze. Dr. Zhang notes that based on the available toxicology data for each excipient used in the Pancreaze drug product, there appears to be no significant safety concern for humans; the exposure assessment indicated that the exposures to all excipients appear to be safe at the specified levels based on the toxicity profile of each excipient. Overall, from a nonclinical perspective, Dr. Zhang concludes that there appear to be no anticipated risks associated with the use of Pancreaze at the proposed clinical doses in patients with EPI.

Dr. Zhang recommends an Approval action based on the non-clinical review of the information submitted in the NDA. Dr. Zhang additionally recommends that the proposed labeling be revised to include the following:

- Section 8.1 of Label (Pregnancy): Wording in the Pregnancy section should be revised to: "Teratogenic effects Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PANCREAZE should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes."
- Section 8.3 of Label (Nursing Mothers): Wording in the Nursing Mothers section should be revised to: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PANCREAZE is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency."
- Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility): Wording in the Carcinogenesis, Mutagenesis, Impairment of Fertility section should be revised to: "Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase."

4.2 Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made.

5. Clinical Pharmacology/Biopharmaceutics

5.1 Issues

The reader is referred to the Clinical Pharmacology Review by Lanyan Fang dated March 15, 2010 for complete information.

The studies reviewed by Dr. Fang and her conclusions are described below:

5.1.1 *In Vivo* Intubation Study (Bioavailability Study)

This was a single-dose, open-label, placebo-controlled, crossover study that evaluated the bioavailability of Pancreaze in 13 patients with EPI; data were available from 12 patients that completed both study periods. Three capsules of Pancreaze MT 21 or placebo were taken with a high-fat liquid test meal; gastric and duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Based on the clinical pharmacology reviewer's calculation, mean relative local bioavailability of lipase in Pancreaze was 19% with a coefficient of variation (CV) of 156%. The clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum. The bioavailability study is not a required study for the NDA approval.

5.1.2 *In Vitro* Compatibility Studies

There were two *in vitro* compatibility studies, one with baby foods, and the other in infant formula.

In Vitro Compatibility Study with Baby Foods: The percentages of lipase activities recovered after mixing Pancreaze content (minitablets) with selected baby foods (applesauce, sweet potato, vanilla and chocolate pudding) were determined. After 15 minutes of contact with baby foods tested and 60 minute dissolution testing in simulated gastric fluid (SGF) at 37 ºC, the mean lipase activity ranged from 97 to 107% relative to that of control. The coefficient of variation (CV%) of remaining lipase activity across three microtablet replicates from all four Pancreaze capsule strengths against all six baby food matrices (applesauce from Gerber and Beechnut, sweet potato from Gerber and Beechnut, vanilla pudding and chocolate pudding) ranged from 0 to 4%. Thus, the pre-specified acceptance criteria (CV% ≤10% and mean remaining lipase activity of 90-110%) were met for compatibility.

In Vitro Compatibility Study in Infant Formula: The clinical pharmacology reviewer noted that although the study was conducted with Nutricia, an infant formula used in the Netherlands that is not widely used in the US, the results are applicable to commercially available formulas used more commonly in the US. The clinical pharmacology reviewer concluded that the test conditions in this *in vitro* study (i.e., high viscosity of formula and weak agitation) may not reflect conditions of use. Thus, the reviewer recommended that the labeling regarding administration with formula or breast milk include a statement such as the following: "Contents of the capsule should not be mixed directly into formula or breast milk."

5.2 Recommendation

An Approval Action is the recommendation by the Clinical Pharmacology discipline.

6. Clinical Microbiology

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

7. Clinical/Statistical - Efficacy

7.1 Issues

The reader is referred to the Clinical Review by Ali Niak dated April 12, 2010, and the Statistical Review by Shahla Farr dated March 1, 2010, for complete information.

Pancreaze has been marketed in the United States since 1988 under the name "Pancrease MT." The manufacturing process and formulation of the product have not significantly changed since that time. The current Commercially Marketed Product (CMP) and the To be Marketed Product (TbMP) are believed to be the same formulation.

In addition, there is considerable clinical experience with similar formulations of porcine-derived PEPs.

7.1.1 Clinical Studies

The pivotal study (PNCRLPCYS3001) and the supportive study (20-101) were reviewed in depth by the Clinical Reviewer. Pertinent features of these studies are summarized in the table below.

Table 3. Pancreaze Clinical Studies

Study No.	Design	Product	Primary Endpoint	No. of Pts	Age	Patient Population
PNCRLPCYS3001	Randomized, double-blind, placebo-controlled	Pancreaze and Placebo	Change in CFA	40	8-57 years	CF
20-101	Randomized, investigator-blinded, dose-ranging study	Pancreaze	Change in CFA	17	6 – 30 months	CF

(Table above is modified from table found in Clinical Review by Ali Niak.)

Study PNCRLPCYS3001 had an open label period prior to the randomized placebo-controlled withdrawal period. Study 20-101 had a run-in period prior to the randomized dose-ranging period.

7.1.2 Efficacy Results

Study PNCRLPCYS3001

This was a multicenter, randomized, double-blind, placebo-controlled study in 40 patients, ages 8 to 57 years, with a confirmed diagnosis of CF and EPI.

Pertinent features of the study design are summarized in the table below.

Table 4. Pertinent Features of Study Design

Study Days	Period*	Treatment
-7 to -1	Screening Period (7 days)	Current PEP / Pancreaze*
0 to 14	Open label Run-in Period (14 days)	Pancreaze
15 to 21	Double-blind Withdrawal Period (up to 7 days)	Pancreaze or Placebo

*Patients transitioned from their current PEP to Pancreaze during the screening period.
(The table above is modified from a figure and supporting text found in the Clinical Review by Ali Niak.)

Doses in this study were individually titrated, and not to exceed a maximum lipase dose of 2,500 lipase units/kg/meal, which is in agreement with CFF recommendations (see Appendix 1). The initial screening dose of Pancreaze was based on the average PEP dose for the three days immediately before entry into the study. During the open-label run-in period, the Pancreaze dose was adjusted to accommodate the high-fat diet (≥ 100 g fat per day ±15% or ≥ 3 g per kg per day for younger subjects not able to achieve 100 g of fat per day) based on clinical signs and symptoms.

Patients with CFA ≥80% in the open label period were randomized to Pancreaze or matching placebo for up to seven days of treatment.

The primary efficacy endpoint was the change in coefficient of fat absorption (CFA) from the open label run-in period to the end of the double-blind withdrawal period. CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet. The formula for Coefficient of Fat Absorption (CFA) is provided below:

CFA [%] = {[Fat intake (g/day) – Fat excretion (g/day)] / Fat intake (g/day)} X 100

Fifty-four subjects were screened for entry into the study; five of these subjects were excluded as screening failures. The remaining 49 subjects were enrolled; one subject withdrew consent. The remaining 48 subjects entered the open label run-in phase; eight subjects discontinued (5 had CFA < 80%; 2 withdrew consent; 1 had an adverse event; and 1 withdrew due to noncompliance). The remaining 40 subjects were randomized in a 1:1 fashion to receive either Pancreaze or placebo. All 40 subjects completed the study.

The demographics of the study are summarized in the table below.

Table 5. Demographics of Study PNCRLPCYS3001

	Placebo (n=20)	Pancreaze (n=20)
Age (n, %)		
7 to 17 years	8 (40%)	6 (30%)
18 to 60 years	12 (60%)	14 (70%)
Gender (n, %)		
Male	13 (65%)	9 (45%)
Female	7 (35%)	11 (55%)
Race (n, %)		
Caucasian	19 (95%)	17 (85%)
Black	1 (5%)	1 (5%)
Other	0	2 (10%)

(Table above is modified from the Clinical Review by Ali Niak.)

In children (7 to 17 years), the mean age was 13 years in the placebo group and 11 years in the Pancreaze group. In adults, the mean age was 30 years in the placebo group and 29 years in the Pancreaze group. The patients were mostly Caucasian (92%) which is consistent with the racial/ethnic prevalence of this disease.

The mean dose during the controlled treatment period was approximately 6,400 lipase units per kilogram per day.

CFA at the end of the open-label run-in period, CFA at the end of the double-blind period, and change in CFA are summarized in the table below.

Table 6. Change in CFA (ITT Analysis Set in Study PNCRLPCYS3001)

Timepoint Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)
Baseline[a]		
N	20	20
Mean (SD)	90.5(4.51)	88.2(5.07)
Median	90.7	88.9
Range	79-99	78-95
End of double blind[a]		
N	20	20
Mean (SD)	56.4(24.93)	86.8(8.09)
Median	59.5	90.7
Range	12-95	63-95
Change from baseline[a]		
N	20	20
Mean (SD)	-34.1(23.03)	-1.5(5.88)
Median	-32.9	-0.0
Range	-75- 0	-16- 8
P-Value[b]		<0.001

[a] Include subjects who had data at the 2 time points. Baseline was measured at Visit 2 (open-label) and end of double-blind was measured at Visit 3.

[b] The p-value is from ANCOVA model with treatment as a factor and baseline percent COA-fat as a covariate.

(Table above modified from Clinical Review by Ali Niak; source of table is page 45 of Clinical Study Report.)

At baseline (i.e., at the end of the open-label run-in period), CFA was similar in both the Pancreaze and placebo groups. At the end of the double blind period, the mean CFA for patients receiving Pancreaze was 87%; the mean CFA for patients receiving placebo was 56%. The mean change in CFA from baseline was -34% in the Pancreaze group, and -1.5% in the placebo group; the difference between the two groups was 33% ($p < 0.001$; 95% CI [22, 43]). The statistical reviewer confirmed the results and was agreement with the Applicant (see Statistical Review by Shahla Farr).

The statistical reviewer conducted analyses by gender and age (see tables below).

Table 7. Analysis of CFA by Gender - Mean (Std)

Gender	Baseline Mean (Std)		End of Treatment Mean (Std)		Change Mean (Std)	
	Pancrease MT	Placebo	Pancrease MT	Placebo	Pancrease MT	Placebo
Female	88.65 (5.9) (n=11)	92.08 (4.7) (n=7)	87.60 (6.6) (n=11)	**74.83 (13.7)** (n=7)	1.05 (5.4) (n=11)	**17.25 (13.2)** (n=7)
Male	87.7 (4.2) (n=9)	89.67 (4.4) (n=13)	85.76 (9.9) (n=9)	**46.43 (24.2)** (n=13)	1.94 (6.7) (n=9)	**43.24 (22.3)** (n=13)

(Table above is taken from the Statistical Review by Shahla Farr.)

The statistical reviewer commented that although both gender subgroups indicate a statistically significant treatment effect ($p<0.001$ for males and $p=0.006$ for females), the female patients in the placebo arm had a smaller decrease in their CFA than their male counterparts.

Table 8. Analysis of CFA by Age Category - Mean (Std)

Age Category	Baseline Mean (Std)		End of Treatment Mean (Std)		Change Mean (Std)	
	Pancrease MT	Placebo	Pancrease MT	Placebo	Pancrease MT	Placebo
Adults (>=18 years)	87.7 (5.4) (n=14)	89.7 (4.5) (n=12)	86.6 (9.4) (n=14)	51.5 (25.5) (n=12)	1.2 (5.9) (n=14)	38.2 (24.4) (n=12)
Children/Adolescent (<18 years)	89.1 (4.4) (n=6)	91.7 (4.6) (n=8)	87.1 (4.5) (n=6)	63.6 (23.8) (n=8)	2.0 (6.4) (n=6)	28.1 (20.8) (n=8)

(Table above is taken from the Statistical Review by Shahla Farr.)

Analysis by age category for adults and children/adolescents showed a non-significant treatment-by-age category interaction ($p=0.5$). The treatment effect within each age category was, however, statistically significant ($p < 0.001$ for adults and $p < 0.02$ for children/adolescents).

Study 20-101

The supportive study, 20-101, was a randomized, investigator-blinded, dose-ranging study of 17 patients, ages 6 months to 30 months with EPI due to CF.

All patients were transitioned from their usual PEP treatment to Pancreaze at 375 lipase units per kilogram body weight per meal for a six day run-in period. Patients were then randomized to receive Pancreaze at one of four doses (375, 750, 1,125, and 1,500 lipase units per kilogram body weight per meal) for five days.

A primary efficacy endpoint was the change in the coefficient of fat absorption (CFA) from the end of the run-in period to the end of the randomized period

The final analysis population was limited to 16 patients; one of the 17 patients that were randomized was excluded due to withdrawal of consent.

The mean age was 18 months; the median (range) of age was 16 months (6 months, 30 months). Approximately two-thirds of the patients were female; all of the patients were Caucasian.

The mean Pancreaze dose in the open label run-in period was 1,606 lipase units per kilogram body weight per day.

CFA at the end of the run-in period, CFA at the end of the randomized period, and change in CFA are summarized in the table below.

Table 3. Change in CFA in Study 20-101 (End of Run-in Period to End of Study)

	375 units lipase/kg/meal n=4	750 units lipase/kg/meal n=4	1,125 units lipase/kg/meal n=4	1,500 units lipase/kg/meal n=4
CFA (%)				
Day 6* (Mean, SD)	93 (2)	90 (5)	81 (11)	93 (3)
Day 11# (Mean, SD)	92 (3)	91 (4)	80 (13)	91 (2)
Change in CFA (%) Day 6 to Day 11 (Mean, SD)	-2 (3)	1 (3)	-1 (3)	-2 (3)

*End of Run-in Period; #End of Study

Patients showed similar CFA at the end of the run-in period as at the end of the study across the four treatment arms.

7.1.3 Dosage Strength Formulations

The four dosage strength formulations are MT 4.2, MT 10.5, MT 16.8, and MT 21 capsules containing 4,200, 10,500, 16,800, and 21,000 USP units (U) lipase respectively. MT 4.2, MT 10.5, and MT 16.8 each have the same ratios of lipase:amylase and lipase:protease; MT 21 has a higher ratio of lipase:amylase and lipase:protease than MT 4.2, MT 10.5, or MT 16.8.

The clinical reviewer noted that both the MT 10.5 and MT 21 formulations were used in the pivotal study (PNCRLYPS3001). Baseline CFA, end of treatment CFA, and change in CFA were summarized in the group that received the MT 10.5 capsule and the group that received the MT 21 capsule. The results suggested that the response was similar to both capsules.

7.2 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical Efficacy standpoint.

8. Safety

The reader is referred to the Clinical Review by Ali Niak dated April 12, 2010 for complete information.

There is extensive clinical experience with porcine-derived PEPs in patients, as these have been in clinical use since prior to 1938. The AE profile of PEPs has been well described in the clinical literature; the long-term safety experience has demonstrated that the PEPs are relatively safe.

The PEP Guidance states that it is not necessary to conduct long-term safety evaluations of PEPs in support of PEP NDAs; this is largely because of the long and extensive safety experience with PEPs. The PEP Guidance however does state that a short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the gastrointestinal tract and are not absorbed, the Guidance further recommends that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms during these clinical trials.

A key exception to the relative safety of PEPS is fibrosing colonopathy (FC):

- Fibrosing Colonopathy: FC is a rare but serious condition that may result in colonic stricture. Most of the cases of FC have been reported in younger children with CF. Although the etiology of FC is not known with certainty, FC has been associated with high dose exposure to PEPs. Consensus guidelines have been established by the Cystic Fibrosis Foundation (CFF) in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[10,11,12] (See also Appendix 1.) Continued monitoring for fibrosing colonopathy that is associated with PEP use is likely to best be performed through global safety surveillance.

Other safety concerns with PEPs are described in the literature, and include the following:

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.

- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g. pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.

[10] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[11] Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[12] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

- Irritation to Oral Mucosa: Disruption of the protective enteric coating, and early release of the enzymes may lead to the irritation of the oral mucosa as well as loss of enzyme activity.

The theoretical risk of viral transmission is summarized below:

- Theoretical Risk of Viral Transmission: There is a concern that because PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[13,14] (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 Issues

The reader is referred to Clinical Review by Ali Niak dated April 12, 2010 for complete information.

8.1.1 Exposure

Clinical Trials (PNCRLPCYS3001 and 20-101): A total of 67 patients were enrolled in the two trials **(**PNCRLPCYS3001 and 20-101**)**, and 66 patients entered the run-in phase and received Pancreaze. Of these 66 patients, 57 were randomized: 20 patients to receive placebo and 37 patients to receive Pancreaze. In Study PNCRLPCYS3001, a 10 year-old patient was administered a dose of 12,399 lipase units/kg/day for the duration of the open-label and randomized withdrawal periods. The patient's dose was based on prestudy levels of PERT required to alleviate steatorrhea as determined by the Principal Investigator. This patient experienced mild abdominal pain throughout both study periods. Abnormal chemistry data at the end of the study included mild elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum phosphate. Abnormal hematology data at the end of the study included mild elevations of hematocrit. No abnormalities from analyses of urinalysis or uric acid were noted.

Postmarketing Exposure: The manufacturer does not have specific data on the number of patients treated with Pancrease MT. However, based on sales data (total sales of (b) (4) capsules; from 1988 to December 31, 2008), and the assumption that (b) (4), the estimated exposure to Pancrease MT is 355,415 person-years. The CMP and the TBMP are believed to be the same formulation.

[13] Antiviral Drugs Advisory Committee (December 2, 2008); <http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiviralDrugs>
[14] Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

8.1.2 Safety Findings

Deaths: No deaths were reported in either of the clinical trials (PNCRLPCYS3001 and 20-101).

SAEs: No SAEs were reported in either of the clinical trials (PNCRLPCYS3001 and 20-101).

Dropouts and/or Discontinuations: One patient in the open-label period of Study PNCRLPCYS3001 discontinued Pancreaze due to mild abdominal pain lasting 3 days; the patients was not randomized into the study. There were no adverse events leading to discontinuation in Study 20-101.

Hypersensitivity Reactions: No hypersensitivity reactions were reported in either of the clinical trials (PNCRLPCYS3001 and 20-101).

Common Adverse Events: In the randomized double-blind period of Study PNCRLPCYS3001 (n=20 in the Pancreaze group; n=20 in the placebo group), the incidence of any AE's (regardless of causality) was higher during placebo treatment (60%) than during Pancreaze treatment (40%). The most common AE's reported were gastrointestinal complaints, which were reported more commonly during placebo treatment (55%) than during Pancreaze treatment (30%). The most common gastrointestinal AE's in the Pancreaze group were abdominal pain (10%), abdominal pain upper (5%), flatulence (5%), dyspepsia (5%), gastric disorder (5%), and vomiting (5%). In the randomized dose-ranging period of Study 20-101 (n=4 in the 375 U lipase/kg/meal group; n=5 in the 750 U lipase/kg/meal group; n=4 in the 1125 U lipase/kg/meal group; n=4 in the 1500 U lipase/kg/meal group), the incidence of any AE's (regardless of causality) was 25% (in the 375 U group), 20% (in the 750 U group), and 50% (in the 1500 U group); there were no AE's reported in the 1125 U group. The most common AE's reported were gastrointestinal complaints: 25% (in the 375 U group), 20% (in the 750 U group), and 25% (in the 1500 U group). The gastrointestinal AE's were: abdominal pain, abnormal feces, and frequent bowel movements (in the 375 U group), constipation (in the 750 U group), and vomiting (in the 1500 U group).

Postmarketing Experience (CMP): Based on a cumulative review of postmarketing spontaneous data reported for Pancrease MT and all other pancrelipase formulations from January 1, 1988 through December 31, 2008, a total of 207, medically confirmed, valid cases were reported for pancrelipase. Sixty-one cases (29%) involved the Pancrease MT formulation. There were 44 cases with a fatal outcome with the majority (57%) involving death due to underlying disease states; the remaining 19 cases did not report a cause of death. Sixteen cases with a fatal outcome were associated with Pancrease MT; 9 cases involved death due to a pre-existing cancer, 2 cases involved death due to an underlying disease state, and no cause of death was reported for the remaining 5 cases. Seventy-four serious non-fatal cases were retrieved with the majority of these cases (46, 62%) occurring in subjects ≤17 years old. Twenty-one (28%) of the 74 serious non-fatal cases involved the Pancrease MT formulation. The most frequently reported events in the serious non-fatal cases were gastrointestinal related events, occurring in 60 cases (81%). Of the gastrointestinal events,

the most frequently reported were fibrosing colonopathy-related events (such as intestinal obstruction and intestinal stenosis, 48 cases), abdominal pain (20 cases), and diarrhea (13 cases). Based on the estimated patient exposure for pancrelipase (all formulations), 1,468,690 person-years, cumulative to 31 December 2008, fibrosing colonopathy was reported very rarely. The estimated postmarketing reporting rate for FC was 3.27/100,000 person-years. All FC-related events that were reported occurred prior to 2002. No new FC-related cases were received since 2002.

Conclusion: The Clinical Reviewer concluded that the AE profile of Pancreaze as described in the individual studies was consistent with the currently described AE profile of PEPs in the medical literature. In general, AEs tended to reflect underlying disease, and were most commonly reported in the gastrointestinal (GI) and respiratory systems.

8.2 Recommendation

The Clinical Reviewer recommended that the Risk Evaluation and Mitigation Strategy (REMS) be required as part of the Pancreaze Approval action. A REMS is recommended to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients (see Section 13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements).

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The application was presented to the Pediatric Research Committee (PeRC) on March 31, 2010; there were also additional clarifications and discussion with the Division subsequent to the meeting. The committee recommended the following with the corresponding rationale:

(1) Waiver ages 0-1 month: Necessary studies are impossible or impracticable because patients are usually not diagnosed before the age of 1 month, so there would not be enough eligible patients in this age range to study.
(2) Deferral from age >1 month - 12 months: Development of an age-appropriate formulation is needed.
(3) Completed for ages >12 months - 17 years: Each of the PEPs was unapproved prior to being submitted under NDA; thus, existing labels for the PEPS not submitted under NDA are not viewed as valid. One body of evidence (a range of study types using all formulations of the pancreatic enzymes) was used to create class labeling. As this is new labeling for each of the PEPs, and because the labels did not previously exist, the studies needed to fulfill PREA are considered as having been completed.

The clinical review team including this reviewer is in agreement with these recommendations.

It should be noted that the deferral for patients age > 1 month to 12 months does not require additional studies; rather, the deferral for this age category is for the development of an age-appropriate formulation (i.e., a capsule containing 2,000 to 4,000 lipase units). Such a formulation will 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.

In addition, it should be noted that published literature data with PEPs in general, not necessarily data with the particular formulation (i.e., Pancreaze), is used to establish that pediatric studies for ages > 12 months to 17 years have been completed.

A related point that deserves mention is that there is no "extrapolation" of efficacy data from one age category to another. Rather, the extensive data from studies in the published literature with a variety of PEP formulations across pediatric age groups constitutes evidence of efficacy for PEPs in the pediatric population; evidence of efficacy for the particular formulation (i.e., Pancreaze) comes from the randomized double-blind placebo-controlled cross-over study using that formulation (i.e., PNCRLYPS3001) regardless of whether it was conducted in a pediatric population, an adult population, or a population that included both adult and pediatric patients. In effect, PNCRLYPS3001 can be considered to be a "bridging study" to the existing body of evidence from the literature for a range of pancreatic enzyme formulations.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

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

11.2 Division of Scientific Investigations (DSI) Audits

The reader is referred to the DSI Review by Khairy Malek, dated March 15, 2010 for complete information.

DSI inspections of two clinical sites of Study PNCRLPCYS3001 were performed; these were Site 001017 (Dr. Mathis; Long Beach, California; n=9) and Site 0010113 (Dr. Platzker; Los Angeles, California; n=8). These sites were selected by the Division because each of these sites had large percentages of the overall study population.

The results of inspection by site are as follows:

- Site 001017 (Dr. Mathis; Long Beach, California; n=9): Source documents for determination of the secondary efficacy parameter of coefficient of nitrogen absorption

(CNA) were not at the site, and thus the secondary efficacy parameter could not be verified. This reviewer (Anil Rajpal) explained to the DSI Inspector (Khairy Malek) that the inability to verify the secondary efficacy parameter of CNA is not considered critical to the evaluation of the application. Thus, the DSI Inspector concluded that although violations were noted in the conduct of the study, these are unlikely to impact the validity of the data, and the data generated at this site can be used in support of the NDA.

- Site 0010113 (Dr. Platzker; Los Angeles, California; n=8): The inspections revealed no significant discrepancies/regulatory violations.

The recommendation by the DSI Inspector is that the data generated by the clinical sites of Drs. Mathis and Platzker appear acceptable in support of the application.

11.3 Drug Shortage

Currently, Creon and Zenpep are the only PEPs that are available on the market that have undergone the NDA review process. There are other PEPs on the market that have not undergone the NDA review process, but these will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010.

Discussions took place with Solvay (the manufacturer of Creon) and with Eurand (the manufacturer of Zenpep) regarding the inventory and production capability of each of the firms after April 28, 2010, in case no other PEPs are approved by that time. In addition, a similar discussion took place with Johnson and Johnson regarding the inventory and production capability of their firm if Pancreaze is approved. Based on the information obtained from each of the calls, it appears that even if Pancreaze was not approved, there would be enough PEPs on the market to meet the needs of patients. Thus, with the approval of Pancreaze, a drug shortage does not appear to be likely.

11.4 Administration via Gastrostomy Tubes

PEPs, including Pancreaze, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Pancreaze via gastostomy tubes, the Applicant has committed to conducting *in vitro* testing (see Section 13.6.1).

12. Labeling

12.1 Proprietary name

A review of the proprietary name "Pancreaze" was performed by Anne Crandall in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance

and Epidemiology (OSE) (see DMEPA Proprietary Name Review dated January 25, 2010). The reviewer concluded that the proprietary name of "Pancreaze" was acceptable.

It should be noted that a previously proposed proprietary name for this product, "Pancrease MT," was found to be unacceptable primarily due to the presence of the United States Adopted Names (USAN) stem, '-ase', in the proposed name.

A label and labeling review was also performed by Anne Crandall in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated February 18, 2010). In addition to a Failure Mode Effects Analysis, an Adverse Event Reporting System (AERS) Database search was conducted because the product is currently marketed.

AERS Search: The AERS search conducted on January 5, 2009, yielded three cases; two cases were excluded from further evaluation because the cases involved product complaints associated with labeled adverse events (excessive bloating, gas and weight loss) due to Pancrease therapy. The third case reported an error due to name confusion between Pancrease and Pacerone. A pharmacy technician filled the prescription on refill with Pacerone and the pharmacist checked the order. The medication error reached the patient, however it is difficult, based on the report, to determine whether the patient took the medicine as it seems the error may have been discovered when dispensed to the patient. An additional AERS Interaction search was run which focused on the products Pancrease and Pacerone. The search used the verbatim "Pancrease%" and "Paceron%" and the tradename "Pacerone". No additional cases were found during this search. It should be noted that this issue was addressed in the DMEPA Proprietary Name Review dated January 25, 2010; the proprietary name "Pancreaze" was deemed to be acceptable.

Failure Mode Effects Analysis: The reviewer concluded that the results of the Failure Mode Effects Analysis indicate that the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. To address these issues, the DMEPA Reviewer provided comments to the Applicant regarding Carton and Container Labeling. Each of the issues was adequately addressed in responses from the Applicant. The DMEPA reviewer concluded that the revisions to carton and container labeling were acceptable.

12.2 Division of Drug Marketing, Advertising, and Communications (DDMAC) Comments

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the proposed proprietary name acceptable from a promotional perspective. This is documented in the Tradename review by Anne Crandall dated January 25, 2010.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The Applicant was requested to revise the label and medication guide to be consistent with the corresponding sections for the most recent drug in the class to be approved, Zenpep. In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMEPA Labeling Review, the DRISK Proposed REMS Review, the DRISK Patient Labeling and Medication Guide Review, the DTP Carton and Container Label Review, and the DDMAC Labeling Review. The reader is referred to each of these reviews for complete information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All the primary review disciplines recommended the product for Approval (AP). This Reviewer concurs with the approval recommendation.

13.2 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.

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

A REMS is recommended with the goal of informing patients about the following serious risks associated with the use of Pancreaze:

- The risk of fibrosing colonopathy
- The theoretical risk of transmission of porcine viral disease.

The REMS element is the following:

- Medication Guide

It should be noted that the REMS for Pancreaze will not include a Communication Plan, or an Implementation System.

The timetable for submission of assessments will be:

- 1st Assessment: 18 months after NDA approval
- 2nd Assessment: 3 years after NDA approval
- 3rd Assessment: 7 years after NDA approval

13.4 Recommendation for Postmarketing Required Pediatric Studies

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

REQUIRED PEDIATRIC ASSESSMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

We note that you have fulfilled the pediatric study requirement for ages 1 year to 18 years for this application. The pediatric requirement for 1 month to 1 year is not fulfilled due to the lack of an age appropriate formulation.

We are deferring submission of an age appropriate formulation. The status must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This requirement is listed below.

1. Deferred requirement for development of an age appropriate formulation for Pancreaze (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 October, 2012.

Submit final reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing requirement must be clearly designated "**Required Pediatric Assessments.**"

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes 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)).

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 the 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 these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

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

   The timetable you submitted on April 9, 2010 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: by June, 2011
   Study Completion Date: by January, 2022
   Final Report Submission: by August, 2022

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

   The timetable you submitted on April 9, 2010 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: by June, 2011
   Study Completion Date: by December, 2021
   Final Report Submission: by September, 2022

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

13.6.1 NDA 22-523 Postmarketing Commitments

(1) Initiate and complete the proposed studies (Protocol #s 04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use.

Final Report Submission: by September 30, 2011

(2) Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the Pancreaze manufacturing process. After 50 lots of low-potency microtablets and 25 lots of high-potency microtablets are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability.

Final Report Submission: by March 31, 2013

(3) Perform *in vitro* studies to determine the feasibility of administering the contents of PANCREAZE (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

13.6.2 DMF 7090 Postmarketing Commitments

(1) Develop and validate an infectious assay for PCV1.

Final Report Submission: by January 31, 2011

(2) Establish lot release specifications for PCV1 for the drug substance.

Final Report Submission: by July 31, 2011

(3) Perform additional monitoring of viral load entering the manufacturing process. The control program will include monitoring for human pathogenic viruses by qPCR. An appropriate control strategy will then be implemented.

Final Report Submission: by July 31, 2011

(4) Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Revise the assays, and submit assay validation data, together with acceptance criteria.

Final Report Submission: by January 31, 2011

13.7 Recommended Comments to Applicant

None.

APPENDIX 1

The CFF Dosing Guidelines (from Borowitz et al., 1995[15]) are provided below:

> "Infants may be given 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding. Although it makes physiologic sense to express doses as lipase units per gram of fat ingested, a weight-based calculation is a practical substitute beyond infancy. Enzyme dosing should begin with 1000 lipase units/kg per meal for children less than age four years, and at 500 lipase units/kg per meal for those older than age 4 years. Enzyme doses expressed as lipase units per kilogram per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two or three snacks per day.
>
> If symptoms and signs of malabsorption persist, the dosage may be increased by the CF center staff. Patients should be instructed not to increase the dosage on their own. There is great interindividual variation in response to enzymes; thus a range of doses is recommended. Changes in dosage or product may require an adjustment period of several days. If doses exceed 2500 lipase units/kg per meal, further investigation is warranted (see discussion of management of CF, below). It is unknown whether doses between 2500 and 6000 lipase units/kg per meal are safe; doses greater than 2500 lipase units/kg per meal should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of absorption.
>
> Doses greater than 6000 lipase units/kg per meal have been associated with colonic strictures in children less than 12 years of age, whether standard-strength enzymes or high-strength pancreatic enzymes were taken. Patients currently receiving higher doses should be examined and the dosage either immediately decreased or titrated downward to a lower range."

Borowitz et al. 2002[16] states:

> "To avoid fibrosing colonopathy, it is recommended that enzyme doses should be less than 2500 lipase units/kg per meal or less than 4000 lipase units/gram fat per day."

FitzSimmons et al. 1997[17] states:

> "A 1995 consensus conference on the use of pancreatic-enzyme supplements sponsored by the U.S. Cystic Fibrosis Foundation recommended that the daily dose of pancreatic enzymes for most patients remain below 2500 units of lipase per kilogram

[15] Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[16] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[17] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations."

APPENDIX 2

Deficiencies in Drug Substance – Items #1 to #5 (from Information Request Letter sent to Nordmark dated June 13, 2008; Master File #7090):

1. You have not provided an adequate description of your risk mitigation plan for adventitious agents. Please provide the following:

    a. Your plan for animal disease surveillance, including how emerging viruses will be assessed and controlled.

    b. A description of the sanitizing/cleaning procedures in place to prevent cross contamination. In particular, we noted that the organ grinder used for the production of pancrelipase is also used to process porcine brain tissue and bovine liver tissue for the production of other pharmaceutical products. Please provide documentation to assure that cleaning procedures have been validated for removal of potential viral and TSE agents. Please include a description of the source of the bovine material. Alternatively, we strongly recommend dedicating a tissue grinder exclusively for the production of pancrelipase.

    c. Please comment on the risk to product quality due to the potential infection of swineherds with parasites.

    d. You stated that porcine pancreatic tissue must be designated for pharmaceutical processing. In a submission to the DMF dated, July 16, 1996, in Appendix D4, on page 108 the pancreatic glands are described as for pharmaceutical use only, not for human consumption. Please clarify the quality standards that distinguish porcine pancreatic glands for pharmaceutical use.

    e. In section 3.2.S.2.3.2 you stated that pancreatic glands originate from European Countries, USA, or Canada. Please clarify whether pancreatic glands are harvested from swine born in these regions, or from swine imported into and slaughtered in these regions. In the latter case, please provide information on the country of origin of the swine.

    f. Please provide a summary of your pancreatic tissue vendor qualification/evaluation program for the last 4 years. The summary should include;
        1. Name and dates of all pancreatic tissue vendor audits.
        2. Quality systems evaluated.
        3. A representative Health Certificate for animal by-products from each of the 12 approved vendors.

2. Regarding the viral inactivation studies please address the following concerns:

    a. According to ICH Q5A, because of the inherent variability of the viral clearance studies, results should be obtained from two independent experiments. However, the viral inactivation studies submitted were not performed as recommended, but rather used material from the same samples in duplicate and not from independent sources. Please provide information on the process's capacity to inactivate viruses from two independent experiments.

b. While you provided two independent results for the spiking experiments using FCV, there is a large difference between the values reported. Furthermore, you provided two calculations of overall FCV inactivation that differed by 8.4 logs without indicating which number you believe best represents process capability. ICH Q5A states that the lower value should be used when evaluating data from independent experiments, which, in this case is consistent with the expected hardiness of the virus. Please elucidate the reasons for such great differences in inactivation of this virus and consider performing additional studies to obtain a more consistent evaluation.

c. Although an evaluation of the toxicity or interference of the test sample on the indicator cells appears to have been performed, no data were submitted to support the dilution factors used for the determination of viral titers. Please submit a brief description of the experiments performed and results obtained for the evaluation of assay interference for test samples from the three process steps assessed in the viral evaluation studies.

d. (b) (4) steps use (b) (4) and may have similar enzyme activities that may lead to an overestimation of viral inactivation when adding the clearance values obtained from each individual process step. Please provide data demonstrating that (b) (4) is solely responsible for the viral inactivation observed since this process step also includes pancreatic enzymes that were reported to be responsible for viral inactivation during the (b) (4) step.

e. Please provide a detailed description of the procedures used for the evaluation of the (b) (4) (b) (4) step and include a discussion on the similarity of the lab scale process to the commercial process.

3. Regarding the Q-PCR tests:

a. Without adequate information on the validation characteristics of the PCR tests, we are unable to fully assess your proposal. Please provide data supporting the validation characteristics of the Q- PCR tests used to estimate viral loads of both enveloped and non-enveloped viruses. Please include information on the selection of the primers, assay specificity, sensitivity (LOQ/LOD), linearity and precision, system suitability criteria (including recovery), along with the SOPs for the test protocols.

4. Regarding the viral infectivity tests:

a. Please provide data supporting the validation characteristics of the viral infectivity assays used in the detection of both enveloped and non-enveloped viruses. Please include information on assay specificity, sensitivity (LOD), linearity and precision. Please submit the SOPs for the test protocols including a description of the system suitability criteria used to establish the validity of routine test results.

5. Regarding your specifications for adventitious agents:

   a. Please revise your specifications to include routine testing for PPV infectivity for all lots and tighten your acceptance criterion to reflect recent manufacturing history.

   b. (b) (4) (b) (4) Please submit a revised viral testing plan that includes monitoring these non enveloped viruses. Please include a calculation of estimated viral load per dose based on the limit of detection of the Q-PCR assay for HEV, EMCV, SVDV, Rota Virus, and Reo Virus.

   c. Although you plan to measure PPV genome equivalents, we do not believe this information will be useful in establishing a robust correlation between genome equivalents and infectivity and therefore do not consider this study necessary.

   d. Please establish a specification for infectious PCV 1 and PCV 2. We believe that the final product should be free of infectious PCV as your historical data has shown.

   e. Based on the ability of the process to inactivate enveloped viruses, you have (b) (4) (b) (4). Please provide a calculation of estimated enveloped viruses per dose based on the limit of detection of the Q-PCR assay and discuss how your proposal provides an appropriate level of control for enveloped viruses. Given the situation, we believe that setting action limits and specifications for the presence of viral genomes and infectious viruses, respectively, provides better control of these viruses. Please comment.

APPENDIX 3

Discussion of the viral DS issues from the first and second cycle of the Zenpep NDA Review (taken from the CDTL Review of Zenpep, NDA 22-210, dated August 21, 2009):

A summary of Items #1 to #5 in the letter to Nordmark, and a summary of the DS reviewer's assessment of the adequacy of the manufacturer's response is presented below.

(1) Risk mitigation plan for adventitious agents. Each of the parts of this item was adequately addressed: (a) The plan for disease surveillance includes a provision that glands are quarantined for at least (b) (4) days thus allowing sufficient time to prevent the release of potentially contaminated glands. (b) There is a dedicated tissue grinder thus addressing the concern about sanitizing/cleaning procedures. (c) Information was provided by the manufacturer that the (b) (4) in the manufacturing process would likely inactivate most parasites. (d) It was confirmed that the porcine glands are generally not considered food items, but are derived from animals fit for human consumption. (e) The manufacturer stated that according to EU regulations, imported animals from Canada or the US must be accompanied by a health certificate (documenting that the animals remained in the territory since birth or at least three months before slaughter), and importation of living pigs is restricted to a limited number of countries (Canada, Switzerland, Chile, Iceland, and New Zealand); the manufacturer also noted that importation of living pigs for slaughtering is not a common event. The response was deemed adequate by the DS reviewer. The DS reviewer noted that on inspection, Nordmark indicated that Eurand specifies that pancreatic glands be obtained only from swine raised in the US or Canada. (f) Details of the gland qualification program were provided, and were deemed adequate by the DS reviewer.

(2) Viral inactivation studies. Each of the parts of this item was adequately addressed: (a) The manufacturer provided results of viral inactivation studies using two independent experiments as requested. (b) The manufacturer was requested to demonstrate consistent results from FCV (Feline Calcivirus) clearance studies; FCV is a model of Hepatitis E Virus (HEV), and HEV is of concern since it is a porcine virus that has been shown to infect humans. The manufacturing process does not demonstrate an ability to remove FCV; thus there is a potential risk that product could be contaminated with HEV. However, because Nordmark implemented a PCR method to test for HEV and will reject lots if HEV is present, the response is acceptable. (c) The DS reviewer determined that there were appropriate controls to account for the potential cytotoxic effect of the PEP test article on cells and the potential interference of the PEP test article on the ability to detect virus. (d) The manufacturer demonstrated that the viral inactivation observed could be attributed only to the (b) (4) and not the enzymes as all protease and lipase activity is lost in (b) (4). (e) The manufacturer described the procedures used for the evaluation of the (b) (4) step; the data indicate that the (b) (4) .

(3) Validation Characteristics of PCR tests. A PMC is recommended; the DS reviewer recommends that Nordmark should increase the sensitivity of the viral PCR assays for DS release testing as a PMC. The DS reviewer notes that critical validation parameters

(e.g., sensitivity, linearity, precision, and recovery) of the PCR tests to detect EMCV, HEV, PEV9, Reo1/3, Rota A, Flu (b)(4), VSV-IND, and VSV-NJ genome equivalents were provided. The DS reviewer further notes that the infectious assay sensitivity is equivalent to that of Creon manufactured by Solvay.

(4) Validation of Viral Infectivity Assays. This item has been adequately addressed. The DS reviewer notes that critical validation parameters (e.g., specificity, robustness, limit of detection) were provided for infectious assays for PPV and PCV2.

(5) Specifications for Adventitious Agents. Four PMC's are recommended; the DS reviewer determined that four parts of this item (a, b, d, and e) were not adequately addressed, but did not preclude approval since each could be addressed as a PMC: (a) The DS reviewer determined that PPV specification could be a PMC, and recommended that PCV2 specification also be included with that PMC. (b) Regarding the revised viral testing plan that includes monitoring for EMCV, Reovirus, and Rotavirus, a validated PCR method will be used to test for each of these viruses; however, the DS reviewer recommends that improvement of assay sensitivity be done as a PMC. (d) Regarding specification for infectious PCV 1 and PCV 2, an assay for PCV1 infectivity is not available, but an assay for PCV2 infectivity was recently validated; the DS reviewer recommends that development of an assay for PCV1 infectivity, and establishing specification for the PCV 2 assay be done as PMC's. (e) Regarding specification for enveloped viruses, Nordmark has developed a genome equivalent assay for the VSV and Influenza virus for routine testing of each lot; the DS reviewer recommends that as a PMC, Nordmark monitor the incoming glands to estimate the potential starting levels for the enveloped viruses. The DS reviewer determined that the remaining part (c) of this item was adequately addressed: (c) Because PPV genome equivalents measurements are not correlated with infectivity, the manufacturer eliminated this measurement.

APPENDIX 4

Deficiencies in Drug Substance – Items #6 to #18 (from Information Request Letter sent to Nordmark dated June 13, 2008; Master File #7090):

6. You are currently using the USP lipase reference standard (lot I1E327, and lot H-1) and the USP amylase and protease reference standard (lot 1E218, lot H, and lot I) to measure enzymatic activities in the drug substance. In regards to reference standard, we have the following recommendations:

   a. Please develop an internal reference standard that reflects the commercial manufacturing process to be used, in addition to the USP pancrelipase reference standard, in all release and stability testing.

   b. Please develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.

   c. Please provide the details of the storage conditions and expiration dating for all reference standards.

7. Please consider establishing and justifying a specification for total starting gland weight used for each manufacturing run as it relates to drug substance lipase yield.

8. We acknowledge your plans to re-examine the production process. Please conduct the study on three consecutive batches. Please specify when you plan to initiate and complete these studies.

9. You stated in section 3.2.S.2.6.1.4 that rejected batches may be reworked depending on the complaint made. Please note that rejected batches may not be reworked or reprocessed and product released under an approved NDA without prior FDA approval.

10. Simethicone emulsion is used in the manufacturing process as an (b) (4) Please include testing and establish limits for simethicone levels in your drug substance release specifications, or provide validation data to support simethicone removal.

11. For release of the drug substance and stability studies specifications have been set for an unknown peak, a (b) (4) peak, (b) (4), and an amylase peak. (b) (4) Therefore, the current release specifications are not adequate. Please establish and justify release specifications for all drug substance RP – HPLC peaks.

12. As part of the RP-HPLC assay validation, please determine how much protein is retained on the column.

13. Please establish and justify a specification for water content for drug substance release and stability testing.

14. You demonstrated that the addition of colipase to 3 lots of drug substance does not increase lipase activity. Thus, colipase does not appear to be limiting for maximum lipase activity. However, it is unclear if the manufacturing process results in consistent levels of colipase in the drug substance. Please include a colipase specification for drug substance release or provide a significant amount of data from lots to support lot-to-lot consistency of colipase levels in the drug substance. A consideration for variability in porcine raw materials should be included in this analysis.

15. To demonstrate that the Pancreatin drug substance matrix does not interfere with the lipase enzyme assay, you (b) (4) with a USP reference standard and demonstrated that predicted lipase activity is measured. Since the USP reference standard is not pure lipase and is likely to contain the same potential inhibitory compounds, purified lipase should also be evaluated in this assay. To ensure that (b) (4) (b) (4) purified lipase should also be (b) (4) and predicted lipase activity should be measured.

16. You have not submitted sufficient information in the DMF to evaluate your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing and establish and justify specifications for critical olive oil components.

17. Please provide a copy of the pancrelipase drug substance label.

18. Please clarify the storage conditions and expiration date that are proposed for the drug substance. Please clarify how you will ensure that the Drug Substance is transported under the appropriate conditions and provide shipping validation data.

APPENDIX 5

Discussion of the non-viral DS issues from the first and second cycle of the Zenpep NDA Review (taken from the CDTL Review of Zenpep, NDA 22-210, dated August 21, 2009):

A summary of Items #6 to #18 in the letter to Nordmark, and a summary of the DS reviewer's assessment of the adequacy of the manufacturer's response is presented below.

(6) USP lipase, amylase, and protease reference standards. Each of the parts of this item was adequately addressed: (a) Regarding development of an internal reference standard that reflects the commercial manufacturing process, a lipase assay internal reference standard was created using the Nordmark manufacturing process; it will be used to qualify future USP lipase standards. The DS reviewer determined that the changes made to the reference standard qualification represent an improvement and are acceptable. (b) Regarding the qualification program, the identity acceptance criteria for number of peaks and peak area has been tightened and is consistent with the acceptance criteria used for lot release. (c) Details of storage conditions and expiration dating for reference standards were provided.

(7) Starting gland weight: Specification for total starting gland weight used for each manufacturing run was provided, and the response is adequate.

(8) Plans to re-examine the production process: The data in the DMF update supports the consistency of the Nordmark pancrelipase manufacturing process; thus, the response to this request is adequate.

(9) Rejected batches may not be reworked or reprocessed: This item was adequately addressed as Nordmark does not plan to reprocess or rework rejected batches. The DS reviewer noted that this is a standard cGMP inspection item, and will be verified on the next inspection.

(10) Testing and limits for simethicone levels: As simethicone emulsion is used in the manufacturing process, the manufacturer was requested to include testing and establish limits for simethicone levels. This was adequately addressed as Nordmark stated it does not plan to use simethicone in the production process.

(11) Release specifications: The deficiency of the release specifications (i.e., specifications had been set for an unknown peak, a (b) (4) peak, (b) (4) peaks, and an amylase peak) has been adequately addressed and the new RP-HPLC specifications are appropriate.

(12) HPLC assay validation: Regarding the request to determine how much protein is retained on the column as part of the RP-HPLC assay validation, the manufacturer clarified that most of the pancrelipase material is not retained on the column thus supporting the use of this test method for identity and impurity analysis.

(13) (b) (4)

(14) Colipase specification for DS release: The manufacturer was requested to include a colipase specification for drug substance release or provide a significant amount of data from lots to support lot-to-lot consistency of colipase levels in the drug substance. The DS reviewer noted that although the actual measurement of colipase levels in the pancrelipase drug substance would have been a more scientifically relevant approach, Nordmark has provided results of a characterization study that indicates that sufficient levels of colipase exist in the API to ensure maximal lipase activity. The DS reviewer concluded that the response is sufficient to address the concern of variability of colipase in the API.

(15) Demonstration of predicted lipase activity: It was demonstrated that predicted lipase activity is measured when (b) (4) with a USP reference standard, but since the USP reference standard is not pure lipase and is likely to contain the same potential inhibitory compounds as the pancreatin drug substance matrix, the manufacturer was requested to also evaluate purified lipase in this assay. The response is adequate as Nordmark has performed the requested characterization studies to demonstrate that lipase-inhibitory compounds are not present in the API.

(16) Olive oil qualification: The manufacturer was requested to provide sufficient information to evaluate qualification results for olive oil testing, and to establish specifications for critical olive oil components. The response is adequate as the requested details of the qualification program have now been included in the DMF and are identical to the European Pharmacopoeia.

(17) DS label: A PMC is recommended. The manufacturer was requested to provide a copy of the pancrelipase drug substance label. The label was provided, but there was no expiration date on the DS label; the DS reviewer recommends that this be addressed as a PMC.

(18) Storage conditions and expiration date: The manufacturer was requested to clarify the storage conditions and expiration date, and how it will be ensured that the DS is transported under appropriate conditions. Data were provided to support stability when subjected to freeze thaw conditions and when stored at 40^{o}C/75% RH for 6 months. Data were also provided to support storage of the DS at 25^{o}C/60% RH for three years. On the April 2009, cGMP inspection of the Nordmark facility the company informed the DS reviewer that Eurand is responsible for ensuring that the pancrelipase is shipped under appropriate conditions. The DS reviewer concluded that the response is adequate.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANIL K RAJPAL
04/12/2010