

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022523Orig1s000**

**SUMMARY REVIEW**

## Division Director Review

<b>Date</b>	April 12, 2010
<b>From</b>	Donna J. Griebel, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	022523
<b>Applicant</b>	McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
<b>Date of Submission</b>	June 23, 2009; Received June 23, 2009
<b>PDUFA Goal Date</b>	April 23, 2010
<b>Proprietary Name / Established (USAN) Name</b>	Pancreaze® / pancrelipase
<b>Dosage Forms / Strength</b>	Delayed release capsules for oral administration 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
<b>Proposed Indication(s)</b>	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Ali Niak, MD/Anil Rajpal, MD
Statistical Review	Shahla Farr, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/Sushanta Chakder, PhD
CMC Review/OBP Review	Howard Anderson, PhD/Emanuela Lacana, PhD/Gibbes Johnson, PhD/Barry Cherney, PhD
ONDQA Biopharmaceutics	Tien-Mien Chen, Ph.D./Patrick Marroum, Ph.D.
Microbiology Review	Bryan Riley, PhD/James McVey
Clinical Pharmacology Review	Lanyan Fang, PhD/Sue-Chih Lee, PhD
DDMAC	Shefali Doshi/Kathleen Klemm
DSI	Khairy Malek/Tejashri Purohit-Sheth, MD
CDTL Review	Anil Rajpal, MD
OSE/DMEPA	Anne Crandall, Pharm.D./Melina Griffis, RPh/Denise Toyer, Pharm.D./Carol Holquist, RPh
OSE/DRISK	Steve Morin, RN, BSN/Jodi Duckhorn, MA/Sharon Mills, BSN, RN, CCRP/Claudia Karwoski, Pharm.D.

OND=Office of New Drugs  
DDMAC=Division of Drug Marketing, Advertising and Communication  
OSE= Office of Surveillance and Epidemiology  
DMEPA=Division of Medication Errors Prevention and Analysis  
DSI=Division of Scientific Investigations

Division Director Review

CDTL=Cross-Discipline Team Leader  
DRISK = Division of Risk Management

## Division Director Review

### 1. Introduction

Pancreaze (pancrelipase) is an enteric-coated, delayed-release, porcine-derived pancreatic enzyme (PEP) intended for treatment of exocrine pancreatic insufficiency (EPI).

My review summarizes the major review conclusions of each review discipline.

### 2. Background

Pancreatic enzyme products (PEPs) are used to treat exocrine pancreatic insufficiency. The most common causes of pancreatic insufficiency are cystic fibrosis and chronic pancreatitis. The predominant clinical manifestations, which are secondary to fat malabsorption, include steatorrhea, abdominal pain and weight loss.

PEPs have been available since prior to the Federal Food, Drug and Cosmetic Act of 1938. They have been marketed without being subject to FDA review. They are derived from pancreas glands harvested from pigs raised for human consumption. Variation in the formulations and manufacturing processes result in variations in drug potency across products and within individual products. PEPs are not interchangeable. The historic lack of manufacturing controls raised concerns regarding product quality, both from a safety and efficacy standpoint. Beginning in 1979 the FDA published a series of notices in the Federal Register that culminated with the 2004 Notice of Requirement for NDA Approval, which stated PEPs must obtain NDA approval within 4 years from the published notice in order to be legally marketed. The *Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs* was published in 2006. In October 2008 a Notice of Extension of the deadline for approval under NDA was published. It stated that manufacturers must have an open IND for their PEP product by April 28, 2008, and an approved NDA by April 28, 2010.

Currently the only approved PEP products are Cotazym, an immediate release PEP that is not marketed in the US, Creon, a delayed-release PEP approved on April 30, 2009, and Zenpep, which was approved August 27, 2009. The Creon NDA was presented at a December 2, 2008 meeting of the Anti-viral Advisory Committee in which viral issues associated with porcine-derived pancreatic enzyme products were discussed. In keeping with the Committee members' discussions and recommendations, the FDA concluded that PEPs should have a Medication Guide to inform patients of the risk of fibrosing colonopathy (which may be increased with high dose exposures to pancreatic enzyme products) and the risk of transmission of a viral disease from these products. Creon and Zenpep were both approved with a Risk Evaluation and Mitigation System (REMS) with Medication Guide.

The applicant reached agreement with the FDA regarding the randomized withdrawal design of the major clinical trial submitted to support the efficacy of Pancreaze, in an End of Phase 2 meeting in January 2008. The trials submitted in support of Creon and Zenpep had cross-over designs.

### 3. CMC/Biopharmaceutics

Pancreaze capsules contain 4200, 10,500, 16,800 and 21,000 USP units of lipase. The other listed active ingredients are protease and amylase. The amounts of each of those component enzymes vary along with the lipase dose, maintaining the same ratios of lipase:amylase and lipase:protease:

- 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

The microtablets, 2 mm in size, are coated to produce the delayed release characteristics of the product, which is intended to assure that the enzymes “survive” exposure to gastric acid. The microtablets are encapsulated in gelatin capsules.

Both the drug substance and the drug product are manufactured by Nordmark, which is the Drug Master File (DMF) holder. The drug substance is the same as that for Zenpep, which was previously approved in August 2009. The product reviewer noted that Pancreaze drug product manufacture involves a (b) (4) step, and that the (b) (4) offers an additional viral and microbial reduction or inactivation step to minimize product contamination.

The Microbiology 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. He recommended approval.

The ONDQA Biopharmaceutics reviewers found the proposed dissolution methodology and specifications acceptable. The biowaiver for the two lower strengths of the product was granted.

The capsules are packaged in amber glass bottles. The bottles for the lowest lipase strength capsule contain a desiccant package.

The product reviewers have recommended approval, with the following postmarketing commitments for the drug substance and drug product:

#### Drug Substance

- 1) Develop and validate an infectious assay for PCV1. (Final Report Submission by January 31, 2011)
- 2) Establish lot release specifications for PCV1. (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)

#### Drug Product

- 1) Initiate and complete the proposed studies (Protocol #s 04020298 and 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. (Final Report December 30, 2010)

The postmarketing commitments for the drug substance are consistent with those included in the approval letter for Zenpep, with the exception of PMC #3 above for the Drug Product, in which the applicant commits to performing *in vitro* studies to determine feasibility of Pancreaze administration via gastrostomy tube.

I concur with the conclusions of the product reviewers regarding the acceptability of the manufacturing of the drug product and drug substance.

## **4. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. In keeping with the *Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*<sup>1</sup>, the applicant

---

<sup>1</sup> 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.

provided published information on the excipients in Pancreaze. The pharmacology/toxicology reviewers found that the available toxicology data for each excipient reveal no significant safety concerns for humans.

## 5. Clinical Pharmacology

The Clinical Pharmacology reviewers evaluated an *in vivo* intubation study designed with the intent to evaluate the bioavailability of Pancreaze in patients with exocrine pancreatic insufficiency, and two *in vitro* compatibility studies. Intubation studies have been found to be 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. The *in vitro* compatibility study with baby foods determined that Pancreaze is compatible with applesauce (Gerber and Beechnut), sweet potato (Gerber and Beechnut), vanilla pudding and chocolate pudding. The *in vitro* compatibility study in infant formula was not conducted with an infant formula widely used in the US (formula from the Netherlands) and the test conditions were determined by the reviewers to not reflect conditions of use. The product label will state that the contents of the capsule should not be mixed directly into formula or breast milk.

I concur with the clinical pharmacology reviewers' conclusion that there are no outstanding clinical pharmacology issues that preclude approval of Pancreaze.

## 6. Clinical Microbiology

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

## 7. Clinical/Statistical-Efficacy

The FDA's *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs* states that "Although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea." One of the examples of an acceptable pharmacodynamic measure provided in the Guidance is "Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection." The major study submitted to this NDA utilized the pharmacodynamic measure coefficient of fat absorption (CFA). The formula for CFA is:

$$\text{CFA [\%]} = \{[\text{Fat intake (g/day)} - \text{Fat excretion (g/day)}] / \text{Fat intake (g/day)}\} \times 100$$

One "pivotal" trial (PNCRLPCYS3001) and one supportive trial (20-101) were reviewed by the clinical and statistical reviewers. These studies are summarized in the table below, which is reproduced from Dr. Rajpal's Cross Discipline Team Leader (CDTL) review.

**Table 1. Summary of Clinical Trial Designs**

Study No.	Design	Product	Primary Endpoint	No. of Pts	Age	Patient Population
PNCRLP CYS3001	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.)

\*CFA = Coefficient of Fat Absorption

The design of Study PNCRLPCYS3001, a randomized withdrawal trial, included an open label period followed by the randomized, placebo-controlled withdrawal period. This is summarized in the following table, which is reproduced from the CDTL review.

**Table 2. Summary of Study Periods in Study PNCRLPCYS3001**

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.)

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 was determined from a 72-hour stool collection while the patient consumed a high-fat diet.

After transitioning from their current PEP to Pancreaze during the 7-day screening period, individual patient doses were further adjusted to accommodate a high fat meal, based on clinical signs and symptoms during a 14-day open label run-in period. At completion of the open label run-in, patients whose CFA was  $CFA \geq 80\%$  were randomized to Pancreaze or matching placebo. Forty-eight subjects entered the open label run-in phase and 40 were randomized. It should be noted that five of the eight patients who entered the run-in phase but were not subsequently randomized, were not eligible for randomization because their CFA was  $<80\%$  in the run-in phase.

The age distribution in the trial is summarized below:

**Table 3. Patient Age Distribution in Study PNCRLPYS3001**

	Placebo (n=20)	Pancreaze (n=20)
Age (n, %)		
7 to 17 years	8 (40%)	6 (30%)
18 to 60 years	12 (60%)	14 (70%)

(This Table is reproduced and modified from the CDTL review)

The summary results of the primary efficacy analysis are shown in the table below, which is reproduced from Dr. Anil Rajpal’s CTDL review.

**Table 4. Primary Efficacy Analysis: Change in CFA (ITT Analysis Set PNCRLPCYS3001)**

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

The Biostatistical reviewer found that the treatment effect was statistically significant in both males and females. However, the females who were randomized to placebo after treatment with Pancreaze experienced less of a decrease in CFA than the males randomized to placebo. Subgroup analyses of adults and children/adolescents revealed a statistically significant treatment effect in both age groups.

In the supportive trial, Study 20-101, seventeen children (ages 6 months to 30 months) with EPI secondary to Cystic Fibrosis were randomized to a range of Pancreaze doses. Investigators were blinded. After a six day run-in period of treatment with Pancreaze 375 lipase units per kilogram body weight per meal, patients were randomized to one of four Pancreaze doses (375, 750, 1,125, and 1,500 lipase units per kilogram body weight per meal) for five days. The primary efficacy endpoint was the change in the coefficient of fat absorption (CFA) from the end of the run-in period (Day 6) to the end of the randomized period (Day 11). The efficacy data for the final analysis population (n=16) are summarized in the table below, which is reproduced from the CDTL review.

**Table 5. 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 <sup>#</sup> (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)

The reviewers recommended that the data from this clinical trial be included in Section 14 Clinical Studies of the product label, with the conclusion that the data showed that the children

studied had a “similar CFA at the end of the run-in period (mean Pancreaze dose of 1600 lipase units per kilogram body weight per day) as at the end of the study across the four treatment arms.”

I concur with the reviewers that the short-term efficacy data from the two trials submitted in the NDA support approval of Pancreaze for treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis or other conditions.

## 8. Safety

There were no deaths and no SAEs reported in either clinical trial (PNCRLPCYS3001 and 20-101). One patient in the open-label period of Study PNCRLPYS3001 discontinued Pancreaze due to mild abdominal pain. There were no discontinuations for adverse events in Study 20-101.

In the randomized double-blind period of Study PNCRLPCYS3001, the most common AEs were gastrointestinal complaints, which were more common with placebo (55%) than Pancreaze (30%). The most common gastrointestinal AE's in the Pancreaze group were abdominal pain (10%), upper abdominal pain upper (5%), flatulence (5%), dyspepsia (5%), gastric disorder (5%), and vomiting (5%).

In the randomized dose-ranging period of Study 20-101 there were 4 children treated with Pancreaze at each dose level, with the exception of the 750 U/kg/meal group, in which 5 patients were treated. The most common AE's were gastrointestinal complaints: 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).

The clinical reviewers concluded that the safety profile observed in these trials was consistent with what is expected in clinical evaluation of PEP products. The reviewers concluded that the type and incidence of adverse events were similar in children and adults.

The medical literature identifies the following safety concerns related to use of PEPS, which were incorporated in the product label under Section 5 Warnings and Precautions:

- a. Fibrosing colonopathy, a rare condition that may result in colonic stricture, has been associated with high dose exposure to PEPs, but the etiology is uncertain. Most cases have been reported in younger children with CF. The Cystic Fibrosis Foundation (CFF) Consensus Guidelines recommend limiting the maximum daily dose of PEPs, not to exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.<sup>2,3,4</sup>

---

<sup>2</sup> Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *J Pediatric Gastroenterology and Nutrition*. 2002. 35:246-259.

<sup>3</sup> Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, *J Pediatrics* 1995; 127:681-684.

<sup>4</sup> FitzSimmons SC, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *NEJM* 1997; 336:1283-1289.

- b. Irritation to oral mucosa by PEPs results from disruption of the enteric coating, which allows early release of the enzymes in the mouth.
- c. Hyperuricemia/Hyperuricosuria associated with PEPs may be due to absorption of porcine purines.
- d. Theoretical risk of viral transmission from PEPs because they are porcine-derived products. Although there may be a risk of porcine viruses being transmitted to humans through PEPs, no viral illness secondary to PEP exposure has been documented. Procedures have been put in place in the Pancreaze manufacturing process to minimize this risk. Although manufacturing processes appear to inactivate most enveloped viruses that could be present in the drug substance, these processes have a limited capacity to inactivate non-enveloped viruses.
- e. Hypersensitivity reactions have been reported with PEPs.

The product label's Subsection 2.1 Dosage, under Section 2 Dosage and Administration, will also state (under "*Limitations on Dosing*") that "Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) 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 fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures, indicative of fibrosing colonopathy, in children with cystic fibrosis less than 12 years of age [*see Warnings and Precautions (5.1)*]. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range."

Based on concerns that exceeding the recommended dose of PEPs can increase the risk of developing fibrosing colonopathy and given the theoretical risk of viral transmission from PEPs, Pancreaze will be approved with a REMS (Risk Evaluation and Mitigation Strategy) with Medication Guide under Section 505-1 of the FDCA, in addition to two post-marketing required studies (PMRs) under section 505(o) of the FDCA. The REMS with Medication Guide and the PMRs are consistent with those that were conditions of approval of Creon and Zenpep. The postmarketing required studies are:

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.  
Final Protocol Submission: June, 2011  
Study Completion Date: January, 2022  
Final Report Submission: 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.  
Final Protocol Submission: June, 2011  
Study Completion Date: December, 2021

Final Report Submission:

September, 2022

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting to discuss this application. However, the review decisions regarding labeling and the Medication Guide were influenced by the Committee deliberations at the December 2, 2008 Antiviral Advisory Committee meeting for Creon, in which the potential viral transmission issues related to porcine derived pancreatic enzyme products were discussed.

## **10. Pediatrics**

As described in Section 7 Clinical/Statistical Efficacy above, both clinical trials (Study PNCRLPYS3001 and Study 20-101) enrolled children. Study PNCRLPYS3001 included children in the age range 7 to 17 years, and Study 20-101 enrolled children ages 6 months to 30 months. The Clinical Trials Experience subsection under Section 6 Adverse Reactions of the label will state “The type and incidence of adverse events were similar in children (8 to 11 years), adolescents (12 to 17 years), and adults (greater than 18 years).” In Section 14 Clinical Studies of the product label, the description of the efficacy data from Study PNCRLPYS3001 (referred to as “Study 1” in the label) will include the statement “There were similar responses to Pancreaze by age and gender.” The trial design and data from the pediatric trial, Study 20-101 (referred to as “Study 2” in the label), will also be presented in this section.

The product label will state, in the Pediatric Use subsection of Section 8 Use in Specific Populations, that short-term safety and effectiveness of Pancreaze were assessed in two clinical trials in pediatric patients with EPI due to cystic fibrosis, and that the ages studied were 6 months to 30 months in one trial, and 8 to 17 years in the other. The safety and efficacy observed in the children treated in Study PNCRLPYS3001 (referred to as “Study 1”) is briefly described in this subsection as: “The safety and efficacy in pediatric patients in this study were similar to adult patients.” The efficacy observed in the pediatric trial, Study 20-101 (referred to as “Study 2”) is briefly described as: “When patient regimen was switched from their usual PEP regimen to Pancreaze, patients showed similar control of their fat malabsorption” This subsection of the label will also state that “The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.”

The application was presented to the Pediatric Research Committee (PeRC) on March 31, 2010. In accordance with the recommendations of PeRC, we have determined that the applicant has fulfilled the pediatric study requirement for ages 1 year to 17 years under the Pediatric Research Equity Act (PREA). We are waiving the pediatric study requirement for birth to 1 month because necessary studies are impossible or highly impracticable. Because patients aren't usually diagnosed before 1 months of age, there would not be enough patients in this age range to study. The pediatric study requirement for 1 month to 1 year has not been fulfilled due to a lack of an age appropriate formulation. This requirement, which is deferred at this time, does not necessitate conduct of a clinical trial, but it does require development of an age appropriate formulation that will allow dosing of the youngest, lowest weight patients, including infants less than 12 months of age who will be administered 2000 to 4000 lipase units per 120 mL of formula or per breast-feeding. Extensive data from the published literature from studies of PEPs in general support the efficacy of Pancreaze in children.

## **11. Other Relevant Regulatory Issues**

The Division of Scientific Investigations (DSI) conducted site inspections of two clinical sites that participated in Study PNCRLPCYS3001. The overall assessment was that the data were acceptable and could be used in support of the NDA.

The clinical reviewer evaluated the financial disclosure and noted no concerns.

There are no unresolved relevant regulatory issues.

## **12. Labeling**

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the name "Pancreaze" acceptable from a promotional perspective. The DMEPA reviewers also found the name acceptable. Although the application originally proposed the proprietary name "Pancreaze MT," it was found unacceptable primarily due to the presence of the United States Adopted Names (USAN) stem, '-ase'.

The applicant revised the label and medication guide to be consistent with the corresponding sections for the most recently approved PEP, Zenpep. The 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 were incorporated in the label negotiations.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action – Approval for the indication "for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions".

- Risk Benefit Assessment – All disciplines have determined that there are no issues that preclude approval of this product at this time. The risk and benefit characteristics of this product are favorable, and I concur with the reviewers’ recommendations that this product should be approved with the REMS described below and the PMRs and PMCs described below.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies -

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for porcine-derived PEPs, including Pancreaze (pancrelipase) Delayed-Release Capsules, to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with high doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

The REMS can be found appended to the approval letter. It consists of a Medication Guide and the timetable for submission of assessments of the REMS. (Further details about the REMS assessment plan can be found in the Approval Letter.)

- Recommendation for other Postmarketing Requirements and Commitments

The approval letter will contain the following Postmarketing Required Studies under 505(o) to address important safety issues associated with PEPs:

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.

Final protocol:	June, 2011
Study completion date:	January, 2022
Final report:	August, 2022

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

Final protocol:	June, 2011
Study completion date:	December, 2021
Final report submission:	September, 2022

In addition, under PREA, the applicant is required to develop an appropriate pediatric formulation for the youngest clinically affected age groups. That requirement is deferred and is:

3. Deferred requirement for development of an age appropriate formulation for Pancreaze (pancrelipase) Delayed-Relayed Capsules 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.

The Applicant has also agreed to Post-Marketing Study Commitments, all related to chemistry/manufacturing of the drug substance and drug product. These commitments presented in Section 3 CMC of this review and can also be found in the Approval letter.

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

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

/s/

DONNA J GRIEBEL  
04/12/2010