

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-175Orig1s000

MEDICAL REVIEW(S)

Medical Officer NDA Memo
Division of Gastroenterology and Inborn Error Products

NDA #:	22-175
Applicant:	Digestive Care, Inc.
(Proposed) Trade Name:	Pertzye
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Dosing Regimen:	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Formulation:	For oral administration
Letter Date/Received Date:	November 18, 2011
PDUFA Goal Date	May 18, 2012
Date Review Completed:	December 23, 2011
Clinical Reviewer:	Marjorie F. Dannis, MD
Team Leader:	Anil Rajpal, MD

The Applicant submitted a 4-month safety update to NDA 22-175 on March 17, 2009, which was reviewed with the original submission.

According to the Applicant, “DCI ceased distribution of its prescription pancrelipase delayed-release capsules (PANCRECARB®) in April 2010. Since the February 2010 NDA resubmission, DCI has not received any product complaints; no additional clinical studies have been performed or initiated; and, there have been no approvals, distribution or use of DCI’s drug product in other countries. In conclusion, there is no new safety information learned about the drug that m(a)y reasonably affect the statements of contraindications, warning, precautions, and adverse reactions in the draft labeling.”

Thus, this reviewer’s conclusions regarding safety have not changed from the conclusions stated in the medical officer review of the original submission dated August 27, 2009. Furthermore, this reviewer agrees that “there is no new safety information learned about the drug that may reasonably affect the statements of contraindications, warning, precautions, and adverse reactions in the draft labeling.”

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/s/

MARJORIE F DANNIS
12/23/2011

ANIL K RAJPAL
12/23/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: January 27, 2011
FROM: Julie Beitz, MD
SUBJECT: Complete Response Action
TO: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules
Digestive Care, Inc.

Summary

Pertzye (pancrelipase) Delayed-Release Capsules are an exogenous source of porcine-derived pancreatic enzymes. Pancreatic enzyme products (PEPs) serve as replacement therapy for digestive enzymes physiologically secreted by the pancreas and have long been considered the main stay of therapy for exocrine pancreatic insufficiency (EPI). Several PEPs, including Pertzye, have been marketed in the US for many years and have not undergone review under new drug applications (NDAs).¹ In 2004, to address concerns about variability in potency across products and within product lines, FDA published a Federal Register Notice which stated that PEPs must be marketed under approved NDAs.

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Pertzye (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions.

Before this application may be approved, satisfactory resolution of the identified chemistry, manufacturing, and controls deficiencies for the drug substance (to be addressed by the DMF holder) and for the drug product (to be addressed by Digestive Care, Inc.) will be required. In particular, for the drug substance manufacturing process, the following must be satisfactorily completed: 1) submission of adequate information supporting a change in the intermediate storage containers, and 2) resolution of ongoing discussions involving proposed modifications to in-process microbial controls and the feasibility of *Bacillus cereus* diarrheal enterotoxin testing. In addition, satisfactory resolution of deficiencies identified during inspections of the drug substance and drug product manufacturing facilities, and resolution of discussions regarding the product label, REMS, and postmarketing study requirements and commitments will be needed.

Dosing

Pertzye (pancrelipase) Delayed-Release Capsules is dosed by lipase units. (b) (4) each containing (b) (4) 8000, or 16,000 USP units of lipase. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Pertzye should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. If approved, product labeling will specify dosing recommendations (b) (4) for children 1-4 years of age, and for patients 4 years of age and older. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

¹ Pertzye has been marketed in the US under the name "Pancrecarb" in three strengths, MS-4, MS-8, and MS-16, since 1995, 2000, and 2004, respectively.

Pertzye (pancrelipase) Delayed-Release Capsules are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Pertzye, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the U S Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. Thus, if approved, the **Dosage and Administration** section of drug labeling will state that “Pertzye is not interchangeable with any other pancrelipase product.”

Regulatory History

On October 27, 2008, Digestive Care, Inc. submitted NDA 022175 and was granted a standard review. Inspection of Digestive Care, Inc.’s drug product manufacturing facility on (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 that involving failure to thoroughly investigate the root cause and identify corrective actions when batches fail, and absent records documenting qualified, approved cleansing procedures for equipment and utensils. Based on these findings, the Office of Compliance recommended withholding NDA approval.

Concurrent with this review, FDA reviewed submissions to DMF (b) (4) from the drug substance manufacturer, (b) (4) which supports this NDA. Inspection of (b) (4) on (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483, involving quality systems, production systems, equipment and facilities, laboratory systems and material systems. Based on these findings, the Office of Compliance recommended withholding NDA approval and that a re-inspection of this facility will be required before NDA 022175 may be approved.² A complete response action for NDA 022175 was taken on August 27, 2009.

A re-inspection of the (b) (4) facility was performed in (b) (4) deficiencies were identified on an FDA form 483. During that inspection, FDA obtained and conducted microbiological testing on samples from three drug substance lots; 4 out of 5 test samples tested positive for *E. coli*. An outside laboratory retained by (b) (4) tested the same lots using the same assay that FDA had used and all were found to be negative. In January 2010, FDA collected additional samples from seven lots; analysis showed that none of the samples tested positive for *E. coli*, but all seven contained low levels of *Bacillus cereus* and one of the seven tested positive for *B. cereus* diarrheal enterotoxin (BDE). (b) (4) retained (b) (4) to retest these lots; they found that all seven lots tested negative for BDE. According to arguments set forth by (b) (4), trace amounts of peroxidase intrinsic to the pancreatin drug substance could interfere with the BDE assay and produce false positive results.

In a review dated April 30, 2010, the Division of Microbiology, CFSAN, did not agree that the positive assay results could represent false positive results. The review further stated that if the drug substance lots were “...made with any level of consistency and the batches are homogeneous, it seems that 7/7 samples would have tested positive...” In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.³ The adequacy of additional, yet-to-be-implemented, microbiologic controls of the drug substance manufacturing process would need to be assessed at a future pre-approval inspection.

On July 29, 2010, Digestive Care, Inc. submitted a complete response triggering a second review cycle. Inspections were conducted of (b) (4) and (b) (4) and FDA form 483s were issued to both firms. There were (b) (4) observations cited for (b) (4), including (b) (4). There were (b) (4) observations cited for (b) (4).

² (b) (4) is the also the drug substance manufacturer for Axcan Pharma US, Inc.’s Ultresa (pancrelipase) Delayed Capsules submitted under NDA 022222, and Viokace (pancrelipase) Tablets submitted under NDA 022542. The recommendation of the Office of Compliance to withhold NDA approval applies to these NDAs as well.

³ See memo dated October 25, 2010, from Reginald Bennett, Jennifer Hait, and Sandra Tallent.

(b) (4)
response dated (b) (4) addressing the deficiencies listed on FDA form 483 dated (b) (4) was not deemed adequate. The Office of Compliance again recommended withholding NDA approval. (b) (4)

A re-inspection of Digestive Care, Inc.'s drug product manufacturing facility on (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 involving quality systems, production systems, equipment and facilities. The Office of Compliance again recommended withholding NDA approval. Satisfactory resolution of these deficiencies is required before this application may be approved.

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, focused on the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Pertzeye (pancrelipase) Delayed-Release Capsules.

Chemistry, Manufacturing and Controls Considerations

Digestive Care, Inc. (b) (4) formulations of Pertzeye capsules containing (b) (4) 8000, and 16,000 USP units of lipase, respectively. The capsules contain small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase and pancrease). The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5.

The previously marketed Pancrecarb MS-16 capsules differed from MS-4 and MS-8 capsules in several ways. (b) (4)

Drug substance (b) (4) During the first review cycle, several CMC deficiencies involving the drug substance were identified and conveyed to (b) (4). At this time, the Division of Therapeutic Proteins has determined that deficiencies involving the capacity of the manufacturing process to clear viruses and monitor viral load can be addressed as postmarketing commitments and do not preclude approval of the NDA. At the most recent inspection of (b) (4) FDA noted the use of (b) (4) blue drums for drug substance intermediate storage. Given that drug substance is stored in (b) (4) extractable and leachable studies, evaluation of product quality, stability

(b) (4)

data, and validation studies to support re-use of the containers are needed. These information requests were conveyed to (b) (4) on October 27, 2010. (b) (4) response received on November 9, 2010, will be reviewed in depth in the next review cycle.

Drug product (Digestive Care, Inc). During the first review cycle, several CMC deficiencies involving the drug product were identified that precluded approval of the NDA. These deficiencies involved the applicant's release testing program, stability testing program, manufacturing process and process validation, acceptance criteria and reference standards, control of excipients, particularly the cellulose acetate phthalate and diethyl phthalate used for (b) (4), a comparison of the currently marketed and to-be-marketed formulations, and discrepancies between manufacturing dates and signature dates on Certificates of Analysis. A total of 17 deficiencies were communicated in the August 27, 2009 complete response letter to Digestive Care, Inc.

In the current re-submission, several of the previously identified deficiencies were adequately addressed by the applicant. The remaining deficiencies involve the applicant's release testing program, stability testing program, process validation, qualification of internal reference standards, and proposed expiry of (b) (4) MS-8 drug products. A newly identified deficiency was identified involving the need to perform accelerated and/or stressed stability studies in the stability testing program. These deficiencies will be conveyed in a complete response letter to Digestive Care, Inc.

Microbiology Concerns

Staff in several divisions and offices in CDER and in CFSAN's Division of Microbiology have determined that the presence of any BDE in the resulting drug product could cause gastrointestinal adverse events, including systemic illness, particularly in immunocompromised patients. (b) (4) could be responsible for *B. cereus* growth and BDE production during drug substance processing. Further, relatively (b) (4) employed at (b) (4) (as compared to other pancreatin drug substance manufacturers) may allow the heat labile toxin to survive processing.

On May 3, 2010, (b) (4) was informed that they will need to implement additional microbiologic controls of the drug substance manufacturing process, and provide 1) a justification for all in-process holding times associated with manufacture of the drug substance, 2) the maximum storage time for the (b) (4), 3) information on total aerobic microbial count (TAMC) alert and action levels at particular points in the manufacturing process, 4) a commitment to test each batch of drug substance for BDE prior to release, and 5) a description of the BDE test method, the validation procedure, and a summary of the supporting validation data.

At a meeting with FDA on May 20, 2010, it was agreed that when the TAMC fell between the alert and action levels of (b) (4) and (b) (4) the materials would be tested for BDE biochemically; this agreement was reflected in an amendment to DMF (b) (4) on June 6, 2010. However, since (b) (4) has been unable to develop a validated assay for BDE detection, the DMF was amended on October 22, 2010 to replace the action and alert levels with a specification of no more than (b) (4) and no more than (b) (4) if the specification is exceeded, the batch will be rejected.

At a meeting held with FDA on November 15, 2010, (b) (4) proposed (b) (4) in-process microbiologic action limits. In addition to the previously specified TAMC limits, batches would be rejected if the TAMC exceeded (b) (4) argued that these in-process controls will be highly effective since detectable BDE is only produced when *B. cereus* counts exceed (b) (4) (b) (4) further stated that BDE (b) (4) cannot be recovered due to (b) (4) suggesting that the positive result from FDA testing could not have been due to the presence of BDE. (b) (4) also speculated that previously reported high in-process microbial counts were not representative of the manufacturing process, but rather the result of microbial contamination of improperly designed sampling ports. (b) (4) has relocated and replaced these ports; these changes were in place at the time of FDA's most recent facility inspection.

At the conclusion of this meeting (b) (4) agreed to submit 1) their current proposal for TAMC testing and arguments why it will prevent BDE formation during manufacturing, 2) results of all efforts to validate a BDE test method in the (b) (4), 3) information that BDE is (b) (4) present in the (b) (4) 4) information regarding changes made in the ports used for sampling pancreatin during the manufacturing process, and 5) information about the pancreatin product made under the previous manufacturing process that is still on the market and what they intend to do regarding these products. (b) (4) response submitted on November 22, 2010, will be reviewed in depth in the next review cycle.

Clinical Pharmacology

Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount. For this reason, a thorough QT assessment for this product has not been requested.

Given the importance of using apple sauce as a means to deliver the capsule contents via feeding tubes or to young pediatric patients who cannot swallow whole capsules, the complete response letter requested that Digestive Care, Inc., repeat the *in vitro* stability study in apple sauce using lipase and amylase assays in which a minimum of five data points are used to assess assay linearity. This request is consistent with other requests made in the letter to enhance analytic methodologies used for lipase and amylase assays. In response to this request, the applicant submitted results of a repeat apple sauce compatibility study, but the report was not deemed complete. In addition, the applicant did not simultaneously run quality control samples to check in-process lipase assay performance. These concerns will be conveyed in the complete response letter.

Efficacy

As with other PEP manufacturers, Digestive Care, Inc., was requested to perform at least one controlled clinical trial with Pertzye to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.⁸ Digestive Care, Inc., conducted two clinical trials.

The short-term safety and efficacy of Pertzye was evaluated in a single double-blind, placebo-controlled crossover trial in 24 patients, aged 8-43 years (11 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either previously marketed Pancrecarb MS-16 or placebo for 6-8 days, followed by crossover to the alternate treatment for an additional 6-8 days. All patients consumed a high fat diet. Pertzye treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ($p < 0.001$).

A second open-label, active-controlled crossover trial was conducted in 19 cystic fibrosis patients, aged 12-27 years, to determine the short-term safety and efficacy of previously marketed Pancrecarb MS-8 compared to the patient's usual pancreatic enzyme product (Creon 20, Pancrease MT-10 or MT-20, Ultrasec MT-12, MT-18, or MT-20). Treatments were dosed at 50% of the usual lipase dose. The mean coefficient of fat absorption on Pancrecarb MS-8 was similar to that on usual enzyme therapy. Results from this trial are difficult to interpret because the trial was open-label, had no washout period between the two crossover treatment periods, and permitted repeated stool collections if initial collections were deemed inadequate. In addition, there was no statistical analysis plan prepared during or after the trial, and no missing data handling or multiplicity adjustment strategies. Given that the applicant has since reformulated this dosage form, this trial will not be relied upon to demonstrate the efficacy or safety of a Pertzye formulation containing 8000 USP units of lipase.

No clinical trial evaluating the safety and efficacy of previously marketed Pancrecarb MS-4 was conducted.

⁸ See <http://www.fda.gov/cder/guidance/6275fnl.htm>

Safety

Delayed and immediate release formulations of porcine-derived PEPs used to treat exocrine pancreatic insufficiency have been generally well tolerated. The most common adverse events reported relate to the patients' underlying disease and are referable to the gastrointestinal tract. Pancreatic enzyme products are not absorbed from the gastrointestinal tract and are not systemically active.

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of PEPs, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. Doses greater than 2,500 lipase units/kg of body weight per meal (or > 10,000 lipase units/kg of body weight per day) should be used with caution. Patients receiving doses higher 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. If approved, a Medication Guide will be required as part of a risk evaluation and mitigation strategy (REMS) for Pertzze that will inform patients of this risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study in Pertzze users to assess the incidence of and potential risk factors for developing fibrosing colonopathy.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Pertzze is not retained in the mouth. Pertzze should not be crushed or chewed or mixed with foods having a pH greater than 4.5 since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Risk of Transmission of Viral Disease to Patients. Like other porcine-derived PEPs, Pertzze is derived from porcine pancreas tissue obtained as a by-product from the slaughter of pigs as a source of food. Audit procedures are in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption and to ensure that legal requirements regarding e.g., hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. Two broad categories of porcine viruses, enveloped and non-enveloped viruses, may be transmissible to humans (i.e., have zoonotic potential). In addition, viruses with zoonotic potential such as HEV, the causative agent for hepatitis E, have recently emerged in pigs. The manufacturing process appears to inactivate most enveloped viruses that could be present in the drug substance but has limited capacity to inactivate non-enveloped viruses.

Although there has been no documentation of viral transmission to humans, FDA's Anti-Viral Advisory Committee concluded that there was a theoretical risk of transmission of viral disease to patients treated with porcine-derived PEPs, including Pertzze. If approved, a Medication Guide will be required as part of a REMS for Pertzze that will inform patients of this theoretical risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study, and be requested to conduct postmarketing commitments to ensure that the manufacturing process effectively controls viral load.

Risk of Hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing Pertzze to patients with gout, renal impairment, or hyperuricemia.

Risk of Severe Allergic Reactions. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported in patients with a known allergy to proteins of porcine origin who are treated with PEPs.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the tradenames (b) (4) "Pancrecarb MS-8", and "Pancrecarb MS-16" are not acceptable. (b) (4)

DMEPA informed the applicant on June 11, 2010, that the proposed alternative tradename "Pertzze" was acceptable. The proposed name will be re-reviewed 90 days prior to the approval of the NDA.

Pediatric Considerations

Pediatric Use. If approved, the **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Pertzze were demonstrated. In addition, the label will 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."

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

At the time of approval, FDA will determine the ages of pediatric patients with cystic fibrosis for which Digestive Care, Inc., has fulfilled the pediatric study requirement. FDA will waive the pediatric study requirement for ages 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, and the small number of patients diagnosed in this age category and their geographic dispersal would make conduct of a study in this age group highly impracticable.

At the time of approval, FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight 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.

Postmarketing Requirements under 505(o)

As described in our letter dated August 27, 2009, we have determined that if this application is approved, Digestive Care, Inc. will be required to conduct the following postmarketing studies for Pertzze (pancrelipase) Delayed-Release Capsules to assess a known serious risk of fibrosing colonopathy and an unexpected serious risk of transmission of viral disease to patients taking Pertzze:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pertzze in the US and to assess potential risk factors for the event.
2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pertzze.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

As described in our letter dated March 19, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act, we have determined that a REMS is necessary for Pertzze (pancrelipase) Delayed-Release Capsules to ensure that the benefits of the drug outweigh the known risk of fibrosing colonopathy associated with higher doses of pancreatic enzyme products, and the theoretical risk of transmission of viral disease to patients.

The applicant submitted a proposed REMS on July 31, 2009, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of the applicant's proposed REMS in the next review cycle.

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/s/

JULIE G BEITZ
01/27/2011

Cross-Discipline Team Leader Review

Date	January 27, 2011
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-175
Applicant	Digestive Care, Inc.
Date of Submission	July 29, 2010
PDUFA Goal Date	January 29, 2011
Proprietary Name / Established (USAN) names	Pertzye® pancrelipase
Dosage forms / Strength	Pertzye® (pancrelipase) delayed release-capsules for oral administration, in USP units <ul style="list-style-type: none"> ▪ [REDACTED] (b) (4) ▪ Pertzye 8,000 lipase/ [REDACTED] (b) (4) ▪ Pertzye 16,000 lipase/ [REDACTED] (b) (4)
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Complete Response (CR) under 21 CFR 314

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1. Introduction

A Complete Response (CR) Letter was sent by the Division on August 27, 2009. This resubmission, received July 29, 2010, is a complete response to that letter, and represents the second review cycle for Pertzye (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP). Pertzye is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

In the first review cycle, deficiencies were identified by the Chemistry, Manufacturing, and Controls (CMC), Clinical Pharmacology, and Clinical disciplines.

CMC deficiencies in the CR letter (Items #1 to #18) were related to: (1) release testing program; (2) stability program; (3) (b) (4) steps; (4) validation studies to evaluate (b) (4) of drug substances; (5) control of (b) (4) activity; (6) qualification program for the olive oil substrate; (7) qualification program for drug substances; (8) internal reference standard reflecting drug product manufacturing process; (9) measurement to ensure accurate lipase activity for the working reference standard; (10) analytical methodologies; (11) information about enteric coating; (12) drug product release test sampling plans; (13) comparison of formulation of the To be Marketed Product (TbMP) to the previously marketed product; (14) process validation information; (15) Certificates of Analysis (COAs) and testing results of excipients used; (16) CMC information for the (b) (4) Ink; (17) discrepancies between manufacturing dates and dates COAs were assigned; and (18) deficiencies in drug substance (separate letter with (b) (4) deficiency items sent to the drug substance DMF holder on August 28, 2009).

The Clinical Pharmacology deficiency item in the CR letter (Item #19) was related to validation of the lipase assay method used in the *in vitro* stability study that used applesauce as a mixing medium.

The Clinical deficiency item in the CR letter (Item #20) was related to the fact that comparability of the (b) (4) proposed formulations ((b) (4) MS-8, and MS-16) was not shown, and that the pivotal study used only the MS-16 formulation. Comparability differences were based on: (b) (4)

It should be noted that on March 24, 2010, the applicant submitted what was intended to be a complete response to the August 27, 2009 action letter. However, because particular CMC deficiency items were not addressed in that submission, it was considered an incomplete response to the action letter; this was communicated to the applicant in an Acknowledge Incomplete Response letter dated April 13, 2010.

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: Four PEPs have been approved under NDA to date:

- (1) Cotazym (NDA 20-580): approved in 1996; not currently marketed
- (2) Creon (NDA 20-725): approved April 30, 2009
- (3) Zenpep (NDA 22-210): approved August 27, 2009
- (4) Pancreaze (NDA 22-523): approved April 12, 2010

Thus, there are three approved PEPs (Creon, Zenpep, and Pancreaze) that are currently commercially available in the US.

Unapproved PEPs: Unapproved PEPs can no longer be marketed effective April 28, 2010. PEPs had been available since prior to the Federal Food, Drug, and Cosmetic Act of 1938;

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.

most PEPs had 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: <ul style="list-style-type: none"> ▪ 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, Zenpep, and Pancreaze: A Risk Evaluation and Mitigation System (REMS) was implemented for Creon, Zenpep, and Pancreaze 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, Zenpep, and Pancreaze. (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, Pancreaze, 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, Zenpep, and Pancreaze.

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.

2.2.2 Regulatory History of Pertzze

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

Table 2. Pertinent Regulatory History of Pertzze

Date	Action
May 1994	Original IND submission*
June 2005	Meeting with the Division to discuss NDA submission requirements
October 2005	Meeting with the Division to follow-up on CMC issues from June 2005 meeting
June 2006	Special Protocol Assessment for Pivotal Study (06-001) submitted
February 2007	Meeting with the Division to discuss CMC requirements for NDA submission
November 2007	Fast Track Designation granted
October 2008	Original NDA 22-175 submitted
August 2009	Complete Response Letter sent
July 2010	Class 2 Resubmission of NDA 22-175

* IND 45223

Three strengths of this product (MS-4, MS-8 and MS-16) were marketed in the United States from 1995, 2000, and 2004, respectively, to approximately the middle of 2010 (see Section 2.2.1) under the name “Pancrecarb.” (b) (4)

See the original Clinical Review by Marjorie Dannis dated August 27, 2009, for details of the Pertzze regulatory history.

Review documents from the first review cycle that were relied on by this reviewer are the following:

- Cross Discipline Team Leader Review by Anil Rajpal, dated August 27, 2009
- Clinical Review by Marjorie Dannis, dated August 27, 2009
- Statistics Review by Freda Cooner, dated July 21, 2009

2.3 Current Submission

The NDA resubmission was received on July 29, 2010. It was classified as a six-month resubmission with a PDUFA deadline of January 29, 2011.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines for this review cycle have all written review documents. The primary review documents relied upon for the current review cycle are the following:

- (1) Clinical Memo by Marjorie Dannis, dated January 14, 2011
- (2) CMC Reviews from the Division of Therapeutic Proteins (DTP):
 - (a) CMC Primary Review by Howard Anderson (DTP), dated January 20, 2011
 - (b) CMC Team Leader Summary Review by Emanuela Lacana (DTP), dated January 21, 2011
 - (c) Addendum to CMC Primary Review by Howard Anderson (DTP), dated January 25, 2011
- (3) ONDQA Biopharmaceutics Review by Tien-Mien Chen dated December 9, 2010.
- (4) Clinical Pharmacology Review by Jang-Ik Lee dated January 13, 2011
- (5) Quality Microbiology Memo by Vinayak Pawar dated January 26, 2011
- (6) Division of Medication Error Prevention and Analysis (DMEPA) Reviews:
 - (a) Label and Labeling Review by Irene Chan dated June 23, 2010
 - (b) Proprietary Name Review by Irene Chan dated June 4, 2010(Note that these reviews were completed before the current review cycle in response to the Applicant's proprietary name request submission, dated March 25, 2010.)

Correspondence that was cited by this reviewer consisted of the following:

- Proprietary Name Request Conditionally Acceptable Letter sent to Digestive Care, Inc. dated June 11, 2010 (signed by Carol Holquist, Director Division of Medication Error Prevention and Analysis [DMEPA])
(Note that this letter was sent before the current review cycle in response to the Applicant's proprietary name request submission, dated March 25, 2010.)

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

3. CMC

The reader is referred to the CMC Primary Review by Howard Anderson dated January 20, 2011, the Addendum to the CMC Primary Review by Howard Anderson dated January 25, 2011, and the CMC Team Leader Summary Review by Emanuela Lacana dated January 21, 2011 for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (b) (4), the Drug Master File (DMF) holder (DMF (b) (4)); the DMF has been cross referenced by Digestive Care, Inc. (DCI) in NDA 22-175. DS is derived from porcine pancreas glands harvested from healthy pigs raised in (b) (4) as human food. The glands are obtained from slaughterhouses, which are under the inspection of the (b) (4). The glands are (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b) (4) which results in pancrelipase DS. The resulting pancrelipase DS is used for manufacture of drug product (DP).

(b) (4) is the DS DMF Holder for Ultresa (NDA 22-222) and Viokace (NDA 22-542) as well as for Pertzye. Thus, there is an extensive regulatory history with the DS DMF Holder because the other NDA's (for Ultresa and Viokace) were originally submitted in July 2007 and October 2009, respectively, and there have been re-submissions of the Ultresa NDA.

The drug substances used in each of the products is summarized below:

- Viokace: DS 1252 ((b) (4) DS 1206)
- Ultresa: DS 1286 ((b) (4) DS 1208)
- Pertzye: DS 1206 and DS 1208

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 review of drug substance viral issues. (b) (4) viral inactivation steps are involved in the DS manufacturing process, including (b) (4). 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 DCI in a process that entails:

(b) (4)

Originally Proposed Dosage Strength Formulations: The (b) (4) dosage strength formulations proposed by the applicant in the original submission were the (b) (4) MS-8, and MS-16 capsules containing (b) (4) 8,000, and 16,000 USP units (U) lipase respectively. Comparability differences between the (b) (4) dosage strength formulations were noted based on:

(b) (4)

Currently Proposed Dosage Strength Formulations: The currently proposed MS-16 formulation is the same as the originally proposed MS-16 formulation. In response to deficiency item #20 in the CR letter (see Appendix 4), the applicant has developed new (b) (4) MS-8 capsules (b) (4) MS-8 capsules contain (b) (4) 8,000 USP units of lipase, respectively. The process validation, release, and stability data for the new (b) (4) MS-8 capsules are

discussed in the Current Review Cycle sub-sections of Section 3 CMC and Section 5 Clinical Pharmacology/Biopharmaceutics of this CDTL Review (see Sections 3.2 and 5.2).

An *in vitro* stability study (food compatibility study) with beads (using the original MS-4, MS-8, and MS-16 capsules) mixed in applesauce was conducted to support the use of applesauce to administer the beads (see Section 5 Clinical Pharmacology/Biopharmaceutics).

Packaging: The MS-8 and MS-16 capsules are packaged in white polyethylene bottles with 100 and 250 counts. [REDACTED] (b) (4). Each bottle contains a desiccant.

3.1 Initial Review Cycle

In the initial review cycle, the review of DS viral issues was conducted by Howard Anderson, the review of DS non-viral issues and the review of the DP was conducted by Wei Guo, and the review of microbiology issues was conducted by Vinayak Pawar. Each of these reviews was summarized in the CDTL review by Anil Rajpal. (Please refer to the CDTL review, and each of the individual reviews for more information.)

Deficiencies identified in each of the reviews are summarized below:

3.1.1 DS Viral Issues (first cycle)

The overall findings of the DS Viral Issues reviewer in the first review cycle were that there were a number of deficiencies that precluded approval (see CDTL Review from the first review cycle).

DS viral deficiency items that were communicated to [REDACTED] (b) (4) were related to (see final wording of Items #17 to #23 in the Deficiency Letter sent to [REDACTED] (b) (4) in Appendix 5): (17) sanitizing procedures to prevent cross contamination between DS batches; (18) development and validation of PCV1 infectivity assay; (19) lot release specifications for PPV and PCV2; (20) estimate of viruses per dose of DS, and proposal for appropriate control; (21) plans for improvement of sensitivity of qPCR assays for selected viruses; (22) risk assessment and control strategy for hokovirus; and (23) risk mitigation plan for new and emerging adventitious agents.

3.1.2 DS Non-Viral Issues (first cycle)

The overall findings of the DS Non-Viral Issues reviewer in the first review cycle were that there were a number of deficiencies that precluded approval (see CDTL Review from the first review cycle).

DS non-viral deficiency items that were communicated to [REDACTED] (b) (4) were related to (see final wording of Items #3 to #16 in the Deficiency Letter sent to [REDACTED] (b) (4) in Appendix 5): (3) forced degradation studies to evaluate suitability of RP-HPLC assay for stability testing; (4) amount

of raw material used in DS 1206; (5) justification for different acceptance criteria for (b) (4) for DS 1206 versus DS 1208; (6) clarification of definition of “finished product”; (7) DS 1206 information including in-process lipase activity, microbial limits acceptance criteria, process validation data, and (b) (4) characterization studies; (8) acceptance criteria for release testing of DS 1206 and DS 1208; (9) acceptance criteria for enzymatic activities and assays to measure product-related substances and impurities; (10) trended stability data of DS 1206; (11) olive oil testing program; (12) enzyme assay method validation reports; (13) expiry for DS 1206 and DS 1208; (14) revisions to the testing program for the 1206 (b) (4) (15) method to ensure accurate and consistent lipase activity for the working reference standard; and (16) lipase activity results using (b) (4).

3.1.3 DP Issues (first cycle)

The overall findings of the DP reviewer in the first review cycle were that there were a number of deficiencies that precluded approval (see CDTL Review from the first review cycle).

Deficiency items for DP issues that were sent to DCI were related to (see final wording of Items #1 to #17 in the CR Letter in Appendix 4): (1) release testing using analytical tests to control for product- and process-related impurities and to monitor particle size, target weight, and capsule disintegration time; (2) stability testing using analytical techniques to monitor product degradation; (3) evaluation of (b) (4) steps; (4) evaluation of whether (b) (4) the 1206 DS and the 1208 DS will result in a homogeneously (b) (4) DS; (5) demonstration that the (b) (4) activity is well controlled; (6) evaluation of the olive oil qualification program; (7) evaluation of the qualification program for incoming 1206 and 1208 drug substances; (8) use of an internal reference standard that reflects the DP commercial manufacturing process; (9) implementation of a method to ensure accurate and consistent lipase activity for the working reference standard; (10) assessment of linearity for the lipase and protease assays using 5 data points rather than (b) (4) data points; (11) request for information regarding the cellulose acetate phthalate and diethyl phthalate used for (b) (4) of the product; (12) request for release test sampling plans; (13) request for a comparison of the Currently Marketed Product (CMP) and the To be Marketed Product (TbMP) formulations; (14) request for process validation report; (15) request for representative Certificates of Analysis (CoAs) and testing results of excipients used; (16) CMC information for the (b) (4) Ink; and (17) discrepancies between manufacturing dates and dates COAs were assigned.

3.1.4 Microbiology Issues (first cycle)

DMF (b) (4) was reviewed by Stephen Langille (Microbiology Reviewer for DMF (b) (4)) in the first cycle as a result of a facility inspection that revealed abnormally high counts of spore forming bacteria in the drug substance (see Microbiology Review by Stephen Langille dated August 27, 2009 filed under DMF (b) (4)). The Microbiology Reviewer reviewed the DS manufacturing process for flaws that could lead to increased numbers of microorganisms.

The Microbiology Reviewer recommended that (b) (4) provide information on selected manufacturing processes. These items were included in a Deficiency Letter to (b) (4) dated August 28, 2009, and were related to (see final wording of Items #1 and #2 in Deficiency Letter to (b) (4) in Appendix 5): (1) washing, processing, and microbiological acceptance criteria for pancreas glands; and (2) information about manufacturing process (including storage time, temperature, and data showing effect of storage on microbial growth).

It should be noted that the Review by Vinayak Pawar (Microbiology Reviewer for NDA 22-175) in the first review cycle did not recommend any comments relating to the microbiology information be communicated to the Applicant (see Microbiology Review by Vinayak Pawar dated May 13, 2009 filed under NDA 22-175).

It should also be noted that the CDTL Review for the first review cycle dated August 27, 2009, included a summary of the microbiology review by Vinayak Pawar, but did not include a summary of the microbiology review by Stephen Langille.

3.1.5 Facility Inspections (first cycle)

DCI Inspection: The field investigator noted deficiencies in the facility inspection of DCI.

(b) (4) Inspection: The Drug Product reviewer noted that a facility inspection of (b) (4) was conducted in (b) (4), and a FDA Form 483 with (b) (4) observations was issued. (See Drug Product Review by Dr. Wei Guo dated August 25, 2009.) Based on the Establishment Evaluation System (EES) report, there is a “Withhold” recommendation for (b) (4) dated August 4, 2009.

Consult with DAIOP: The Division of Anti-infective and Ophthalmology Products (DAIOP) was consulted because of findings from the (b) (4) inspection described above related to microbial contamination. The consult memo by Dr. Benjamin Lorenz is provided in Appendix 3. The consult was filed under NDA 22-222 (Ultresa) as (b) (4) is the DS manufacturer for that product as well as for Pertzeye. The conclusions of Dr. Lorenz were as follows:

“The contamination by these (b) (4) organisms varied by lot and stage of processing. The consequence of ingesting this drug product orally with the levels of contamination found is difficult to predict. Since most of these organisms are likely (b) (4) it is not surprising the array of organisms that were found. These organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans, so it may not necessarily constitute a significant risk for most immunocompetent individuals. Of the organisms found, the most concerning are the *Bacillus* spp., the effects of which might only predictably produce mild diarrhea. However, in patients with neutropenia, other major immunocompromise or anatomic derangements (as may be the case in patients with cancer or chronic pancreatitis), the risk could entail systemic illness. Since manufacturing levels exist for these particular organisms, and potentially immunocompromised patients may be exposed,

the appropriate measures should be instituted to rectify this. Consider testing the final product for microbial and toxin contamination as well.”

Upon further discussion at a meeting that included Dr. Lorenz, it was determined that it would not be feasible to test the final product for microbial and toxin contamination.

3.2 Current Review Cycle

The reader is referred to the CMC Primary Review by Howard Anderson dated January 20, 2011, the Addendum to the CMC Primary Review by Howard Anderson dated January 25, 2011, and the CMC Team Leader Summary Review by Emanuela Lacana dated January 21, 2011 for complete information.

3.2.1 DS Viral Issues (current cycle)

Many of the DS viral issues identified in the first review cycle of Pertzze have been addressed in the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF. In the most recent review of DS viral issues (dated April 28, 2010; filed under NDA 22-222), the DS Viral Issues Reviewer (Howard Anderson) concluded that deficiencies exist, but did not preclude approval of that application since these could be addressed as postmarketing commitments (PMC's) (see CDTL Review of Ultresa NDA dated May 5, 2010 for complete information). It should be noted that another DS Viral Issues Review has not been conducted since the time of the last review because updates regarding DS viral issues have not been provided in the DMF for (b) (4) (DMF (b) (4)).

PMC's: The PMC's recommended by the DS Viral Issues reviewer are provided below. These PMC's will be planned for negotiation with the Applicant should Pertzze receive an Approval action during a subsequent review cycle (see also Section 13.6).

- PMC #1: Submit the final study reports of the cleaning agents effectiveness for viral inactivation for protocols # 09-VV-17-020 & 09-VV-12-121 to the FDA. (Final Report Submission date to be determined as per review.)
- PMC #2: Submit the validation report for the PCV1 (Porcine Circovirus 1) infectivity release assay to the FDA. (Final Report Submission date to be determined as per review.)
- PMC #3: Establish lot release specifications for the PCV1 infectivity assay. (Final Report Submission date to be determined as per review.)
- PMC #4: Establish lot release specifications for the PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) infectivity assay. (Final Report Submission date to be determined as per review.)
- PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide better assurance that released drug substance will not contain

EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reo Virus), Rota (Rota Virus), PTV (Porcine Teschovirus) viruses. Revise the assays, and submit assay validation data, together with acceptance criteria. (Final Report Submission date to be determined as per review.)

PMC #6: Submit the plan to assess the risk to product quality associated with porcine hokovirus and the control strategy to the FDA. (Final Report Submission date to be determined as per review.)

3.2.2 DS Non-Viral Issues (current cycle)

Many of the DS non-viral issues identified in the first review cycle of Pertzze have been addressed in the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF.

In the most recent review of DS non-viral issues (dated October 13, 2010; filed under NDA 22-222 for Ultresa), the DS Non-Viral Issues Reviewer (Wei Guo) concluded that each of the deficiencies identified in the previous cycle of that application was adequately addressed. However, the secondary CMC reviewer identified additional deficiency items (see CMC Secondary Review by Emanuela Lacana dated January 21, 2011):

- (1) During inspection of (b) (4) inspectors noted that changes to the drug substance intermediate container were introduced in the process, and the DMF holder was cited for lack of extractable leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported, however (b) (4) did not provide validation data or extractable/leachable studies for the new container. (See **Item #6** in Section 13.1.2 of this CDTL review.)
- (2) Both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase from (b) (4) for the presence of Bacillus cereus diarrheal enterotoxin and detected the toxin in several samples. (b) (4) claims that the results are false positive and that the false positive results are due to (b) (4) interference. However, the DMF holder has provided no data to support this contention. (See **Items #7 to #14** in Section 13.1.2 of this CDTL review.)

3.2.3 DP Issues (current cycle)

The overall findings of the DP reviewers in the current review cycle were that although the majority of the deficiencies identified in the first cycle were adequately addressed, there were some deficiencies that still existed and that precluded approval; the secondary CMC reviewer identified an additional deficiency item. (See CMC Primary Review by Howard Anderson dated January 20, 2011, Addendum to CMC Primary Review by Howard Anderson dated January 25, 2011, and CMC Secondary Review by Emanuela Lacana dated January 21, 2011 for complete information).

The additional deficiency item identified by the secondary CMC reviewer was as follows:

- Your annual stability program for drug product provides for one lot of material to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions may not be adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. Please incorporate accelerated and/or stressed stability studies in your annual stability program for drug product.

(See also **Item #6** in Section 13.1.1 of this CDTL Review.)

A summary of the CMC Reviewers' assessment of the adequacy of DCI's response to Items #1 through #17 in the CR Letter dated August 27, 2009 (see Appendix 4) is presented below.

- (1) Release Testing Program. Deficiency items should be communicated to DCI; the primary CMC reviewer determined that one part of this item (a) was not adequately addressed:
 - (a) Although the applicant provided assay development reports and validation and method transfer reports for a RP-HPLC assay to be included in the release and stability programs, there are still the following deficiencies: (i) acceptance criteria are for six enzyme peaks and for impurities peaks, and should be revised for all measurable peaks (see **Item #7a** in Section 13.1.1 of this CDTL Review); (ii) acceptance criteria based on testing results of two 30-month old lots would allow for a large loss of enzyme activity over the shelf-life and should be revised (see **Item #7b** in Section 13.1.1); (iii) information on sample recovery and validation studies supporting column use and reuse was not provided (see **Item #7c** in Section 13.1.1); (iv) a standard operating procedure was not provided for the DCI assay (see **Item #7d** in Section 13.1.1); and (v) a drug product reference standard, a description of procedures to quantify impurities levels, and stability data for (b) (4) were not provided for the (b) (4) assay (see **Item #7d (i), (ii), and (iii)** in Section 13.1.1).

The primary CMC reviewer noted that the next part (b) of this deficiency item was adequately addressed:

 - (b) The applicant provided appropriate analytical tests to monitor particle size, target weight of pellets/capsule and capsule disintegration time.

Regarding the last part (c) of this deficiency item, the primary CMC reviewer noted the following:

 - (c) Dissolution is being reviewed by the ONDQA Biopharmaceutics Reviewer (see Section 5.2.2 of this CDTL Review).
- (2) Stability Testing Program. Deficiency items should be communicated to DCI; the primary CMC reviewer determined that three parts of this item (a, b, and e) were not adequately addressed:

- (a) The HPLC method is inadequate and was discussed under the Release Testing Program in 1.
- (b) The protease and amylase acceptance criteria do not specify an upper limit (see **Item #3a** in Section 13.1.1). The proposed (b) (4) lipase activity stability acceptance range is significantly different from the acceptance range (b) (4) activity) for lot release and has not been adequately justified (see **Item #3b** in Section 13.1.1). The significantly different stability data observed for a particular lot (lot PC-6H05B) compared to the other two lots should be commented on by the applicant and may necessitate testing of additional lots (see **Item #3b (i)** in Section 13.1.1). The observed trend of (b) (4) lipase activity over time of the MS-16 product during storage should be commented on by the applicant (see **Item #3b (ii)** in Section 13.1.1).
- (e) Real-time stability data for the (b) (4) MS-8 drug products to support the proposed (b) (4) expiry were not provided (see **Item #4** in Section 13.1.1). The primary CMC reviewer noted that there are issues with the RP-HPLC and the dissolution methods that may have implications for the stability program and proposed expiry.
- Other parts of this deficiency item (c, d, f, g, and h) were adequately addressed:
- (c) The applicant provided updated data indicating that there is not (b) (4) trending of the dissolution data for three lots of MS-16, and one lot of (b) (4) MS-8 drug products. The primary CMC Reviewer commented that this suggests that this product quality attribute is stable over the (b) (4) time period of storage. The primary CMC Reviewer noted that the dissolution assay methodology is being reviewed by the ONDQA Biopharmaceutics Reviewer (see Item 1c above); one of the comments from the Biopharmaceutics discipline to be communicated to the applicant will be about the dissolution assay methodology (see comment #1 in Section 5.2.2 of this CDTL Review).
- (d) The applicant provided updated acceptance criteria for (b) (4), where the individual peaks are measured separately rather than bulked together.
- (f) The applicant stated that (b) (4) will not be used for manufacture of the drug product thus obviating the need for additional data for the (b) (4).
- (g) The requested information (i.e., photostability and forced degradation studies to support in-use stability of drug product) was provided.
- (h) The (b) (4) testing was performed, and showed that the product remained within specifications for the (b) (4) test.
- (3) Evaluation of (b) (4) Steps. This item was adequately addressed as the applicant has removed the options for (b) (4) for this product.
- (4) Evaluation of (b) (4) Homogeneity. This item was adequately addressed as the applicant provided data to support (b) (4) homogeneity of DS 1206 and DS 1208.
- (5) Demonstration that the (b) (4) Activity is Well Controlled. This item was adequately addressed as the applicant provided data demonstrating that sufficient amounts of (b) (4) are present to ensure maximal lipase activity. The study conducted provided for addition of purified (b) (4) in pancrelipase preparation. The data showed that

lipase activity did not increase with addition of (b) (4), indicating that lipase was already saturated with endogenous (b) (4).

- (6) Evaluation of the Olive Oil Qualification Program. This item was adequately addressed as the applicant characterized the olive oil from two different vendors by Thin Layer Chromatography and RP-HPLC. The secondary CMC Reviewer noted that the applicant is now using the RP-HPLC method to evaluate the olive oil and is setting acceptance criteria for 15 characteristic peaks, to be compared to an olive oil reference standard.
- (7) Qualification Program for Incoming 1206 and 1208 Drug Substances. This item was adequately addressed as the applicant provided an adequate qualification program for the 1206 and 1208 drug substances.
- (8) Use of an Internal Reference Standard. A deficiency item should be communicated to DCI. The primary CMC reviewer determined that the reference standard qualification program is an improvement but is deficient in that it does not contain an assay (e.g. RP-HPLC) to monitor for product related impurities. Acceptance criteria should be (b) (4) than the release acceptance criteria and should be based on manufacturing history and clinical experience. Upper limits should be established for the protease and amylase specifications. (See **Item #5** in Section 13.1.1.)
- (9) Implementation of a Method to Ensure Accurate and Consistent Lipase Activity for the Working Reference Standard. The primary CMC reviewer determined that this item was adequately addressed. The primary CMC reviewer noted that there have historically been problems with the USP Pancrelipase Reference Standard that have impacted all PEP manufacturers, and that the current method used by DCI quantifies activity relative to a reference standard and therefore can still be impacted by the use of an inaccurate reference standard. The primary CMC reviewer added that all PEP manufacturers have been encouraged to develop a lipase assay based on absolute units to minimize inaccuracies with the assay, but FDA is not requiring at this time that an assay be implemented for lipase activity based on absolute units for approval of NDAs.
- (10) Analytical Methodologies. This item was adequately addressed. (a) The applicant provided an assessment of linearity for the lipase and protease assays using 5 data points rather than (b) (4) data points. (b) The acceptance criteria for lipase assay linearity were clarified. (c) The amounts of (b) (4) used during assay validation were provided.
- (11) Information Regarding the (b) (4). This item was adequately addressed as the applicant provided information regarding the cellulose acetate phthalate and diethyl phthalate used for (b) (4) of the product. The primary CMC reviewer noted that this product does not contain (b) (4) and that for PEP products the only phthalate that remains a concern is (b) (4) since high levels of it may cause disruption of endocrine function.

- (12) Request for Release Test Sampling Plans. This item was adequately addressed as the applicant provided the requested information; the primary CMC reviewer noted that the applicant is adequately sampling the drug product as samples are taken throughout the process.
- (13) Request for a Comparison of the Currently Marketed Product (CMP) and the To be Marketed Product (TbMP) Formulations. This item was adequately addressed as the applicant provided the requested information; the primary CMC reviewer noted that the MS-16 formulation and the (b) (4) TbMP are identical.
- (14) Request for Process Validation Report. This item was not adequately addressed and a deficiency item should be communicated to DCI. The primary CMC reviewer noted that the lack of process validation for the (b) (4) MS-8 products and only retrospective validation studies for the MS-16 product represent major deficiencies that need to be addressed before this NDA can be approved (see **Item #2** in Section 13.1.1).
- (15) Request for Representative Certificates of Analysis (CoAs) and Testing Results of Excipients Used. This item was adequately addressed as the applicant provided the requested information.
- (16) CMC Information for the (b) (4) Ink. This item was adequately addressed as the applicant provided the requested information; this information was originally requested to determine the amount of (b) (4) in each capsule. The primary CMC reviewer noted that the FDA allowable limits for synthetic (b) (4) for ingested drugs is < 5 mg/day, and that in a gelatin capsule (b) (4) the ink weight is approximately (b) (4) and therefore well below the maximum allowable FDA limits.
- (17) Discrepancies between Manufacturing Dates and Dates COAs were Assigned. This item was adequately addressed as the applicant provided the requested information. The primary CMC reviewer noted that the applicant has demonstrated that material is tested and released within a reasonable time period from the date it is manufactured.

3.2.4 Microbiology Issues (current cycle)

Many of the microbiology issues identified in the first review cycle of Pertzze have been discussed in the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF.

A number of microbiology deficiency items were included in a deficiency letter sent to (b) (4) on May 3, 2010 (see Appendix 6).

In recent reviews of microbiology issues (see Microbiology Review by Stephen Langille dated June 9, 2010 filed under Master File (b) (4) and Addendum dated November 24, 2010 filed under NDA 22-222), the Microbiology Reviewer concluded that the responses to each of the deficiency items in the letter sent to (b) (4) May 3, 2010 were satisfactory; however, the

Microbiology Reviewer concluded that the associated NDA cannot be recommended for approval until the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) (see Section 13.1.2 of this CDTL Review) have been adequately addressed.

Vinayak Pawar (Microbiology Reviewer for NDA 22-175) stated in a memo dated January 26, 2011, that NDA 22-175 cannot be recommended for approval until the product quality microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) have been adequately addressed.

Response to Deficiency Items #1 to #6 (in May 3, 2010 letter):

A summary of the Microbiology reviewer's assessment of the adequacy of (b) (4) response to Items #1 through #6 in the Letter to (b) (4) dated May 3, 2010 (see Appendix 6) is presented below.

- (1) Justification for in-process holding times (especially prior to (b) (4) step). (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) provided the processing and holding times and conditions for the 1206 and 1208 manufacturing processes.
- (2) In-process total aerobic microbial count (TAMC) alert and action levels (for 1206 and 1208). (b) (4) response to each of the parts of this item was deemed satisfactory by the Microbiology Reviewer. (a) The (b) (4) samples alert level proposed was (b) (4) CFU/g and the action level proposed was (b) (4) CFU/g. The Microbiology Reviewer noted that an incoming gland microbial limit acceptance criterion has not been established, but the DMF holder has committed to (b) (4). The Microbiology Reviewer also noted that (b) (4) will track the microbial counts of incoming glands to determine which practices and slaughterhouses provide the greatest control of gland bioburden. (b) The action limit proposed for (b) (4) pancreatin and for the finished drug substance was no more than (b) (4). (c) Exceeded in-process alert levels of (b) (4) will result in a Bacillus diarrheal enterotoxin (BDE) test; a positive BDE test will result in an out of specification (OOS) investigation confirmation of the test results, corrective action, and rejection of the batch. An exceeded in-process action limit of (b) (4) TAMC will also result in an OOS investigation and rejection of the batch following confirmation of the results.
- (3) Explanation for wide range of TAMC (b) (4) (for 1206 lots) and corrective actions. (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) stated that the wide range of TAMC is due to the (b) (4). The following corrective actions were provided to ensure acceptable bioburden levels (b) (4).

The Microbiology Reviewer

commented that although it is possible that (b) (4) could account for the wide fluctuations in TAMC observed in different lots of 1206 Pancreatin, it is not the only possible explanation since the 1208 manufacturing process, which uses a (b) (4) also showed varying microbial counts. However, the Microbiology Reviewer concluded that implementation of (b) (4) microbial limits do represent significant improvements to the manufacturing process.

- (4) Rationale for selection of (b) (4). (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) agreed to (b) (4) for the 1206 manufacturing process, and provided a revised 1206 manufacturing protocol.
- (5) Request to provide the maximum storage time for the 1208 (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) stated that the maximum storage time for the 1208 process is no more than (b) (4), and provided a summary of the microbiological studies to support the proposed (b) (4) hold time. The Microbiology Reviewer commented that although a maximum holding time of (b) (4) is not considered ideal, the (b) (4) is stored in the presence of the (b) (4) and is unlikely to support microbial growth; he further noted that the (b) (4) will be tested for TAMC (b) (4), and that the action level is no more than (b) (4).
- (6) Commitment to test Bacillus cereus enterotoxin prior to release including description of methods and validation. (b) (4) response to each of the parts of this item was deemed satisfactory by the Microbiology Reviewer. (a) (b) (4) stated in an amendment dated June 6, 2010, that the Bacillus cereus enterotoxin test will be a finished active pharmaceutical ingredient (API) release test for the 1206 and 1208 product. (b) A three tiered algorithm for enterotoxin testing was provided in the June 6, 2010 amendment. The initial test will be done using the 3M TECRA BDE test. If this test is positive, an OXOID-RPLA test will be used to confirm the results of the TECRA test. A positive OXOID-RPLA test will result in a "Positive" report for the sample. A negative OXOID-RPLA test will result in verification of the negative results with a Western blot assay. A positive Western blot will be reported as a "positive" sample result. A negative Western blot will be reported as a "negative" sample result. (b) (4) states that this test algorithm was implemented due to the high incidence of false positive results normally obtained using the TECRA and OXOID-RPLA tests. The Microbiology Reviewer noted that the proposed BDE testing algorithm was judged to be acceptable by food safety experts from CFSAN. The Microbiology Reviewer further noted that as of June 6, 2010, the OXOID test and Western blot assay have not been validated to test for the presence of the BDE toxin. Therefore, it was agreed upon in a meeting with Axcan held May 20, 2010 (that included members of both Axcan and (b) (4)) that the TECRA will be used as the release test until the OXOID and Western blot tests have been validated and the validation studies submitted to the FDA (see Response to Question 15 in Memo by Stephen Langille dated May 26, 2010 filed under NDA 22-222; also see Meeting Minutes dated June 18,

2010). A summary of the validation studies supporting the TECRA test was provided in a submission from (b) (4) dated May 28, 2010.

Deficiency Items (in October 27, 2010 letter):

Deficiency items in the October 27, 2010 Letter to (b) (4) are provided in Section 13.1.2 of this CDTL Review.

3.2.5 Facility Inspections (current cycle)

Information from Establishment Evaluation System (EES) reports for each of the facility inspections (for DCI, (b) (4), and (b) (4)) is summarized below, followed by a summary of observations cited in FDA Form 483 for each of the firms.

It should be noted that a Health Hazard Evaluation (HHE) Review was conducted by Anil Rajpal (dated February 23, 2010) because of findings from an (b) (4) inspection related to microbial contamination. A summary of the HHE Review is provided in Appendix 7 of this CDTL Review.

It should also be noted that the Office of Compliance issued (b) (4).

Establishment Evaluation System Reports:

DCI: Based on the Establishment Evaluation System (EES) report, there is a “Withhold” recommendation from the Office of Compliance for DCI dated January 25, 2011.

(b) (4): Based on the Establishment Evaluation System (EES) report, there is a “Withhold” recommendation from the Office of Compliance for (b) (4) dated November 18, 2010.

(b) (4) Based on the Establishment Evaluation System (EES) report, there is a “Withhold” recommendation from the Office of Compliance for (b) (4) (contract testing laboratory for (b) (4)) dated September 22, 2010.

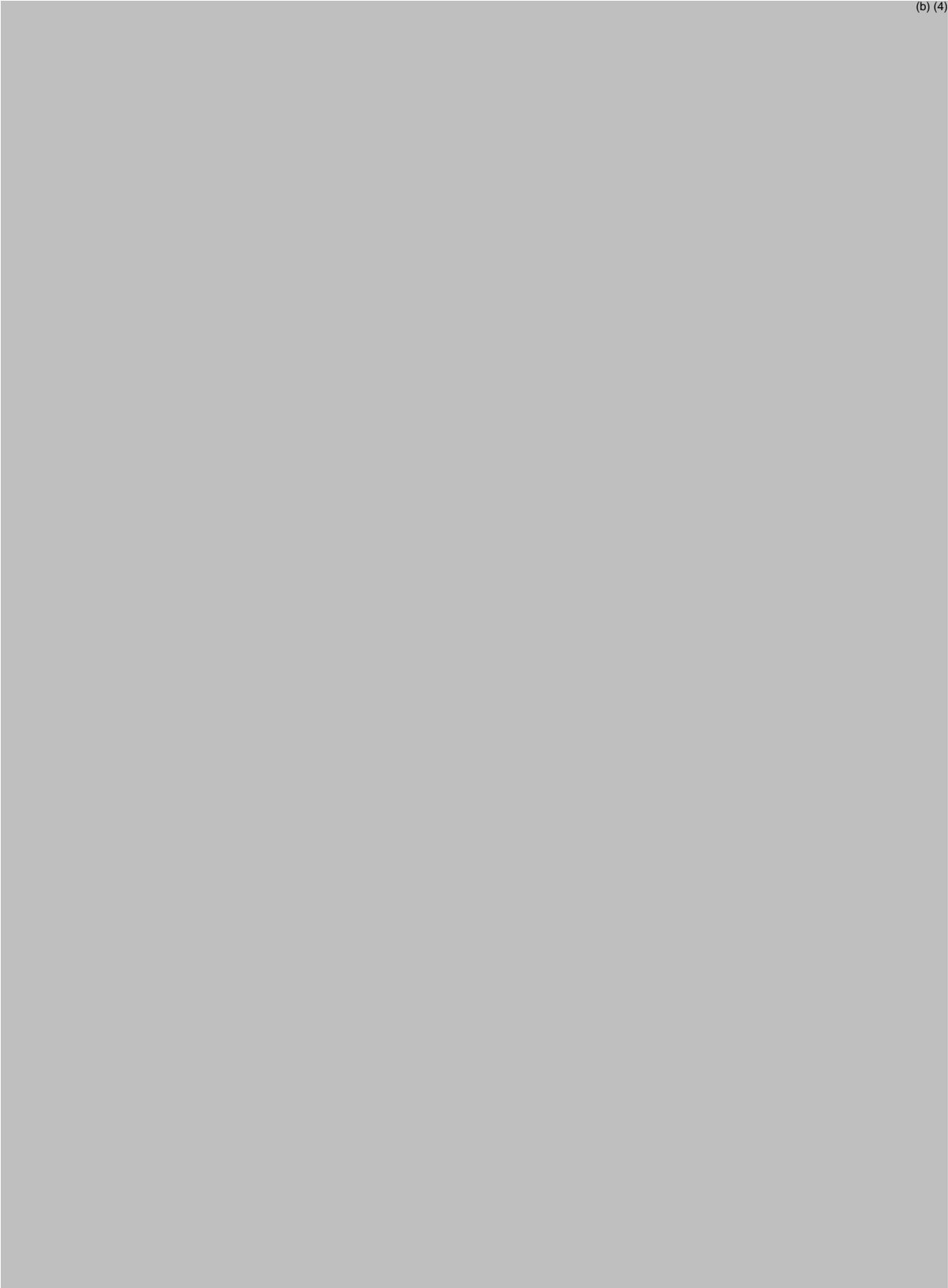
Observations Cited in FDA Form 483:

(b) (4)

(b) (4)



(b) (4)



3.3 Final Recommendation

A Complete Response Action is the overall recommendation by CMC.

The CMC Reviews note that there are deficiencies identified in the NDA and in the DMF that preclude approval of this application. The DP issues should be communicated to the Applicant in the CR letter; the DS issues have been communicated separately to the DMF Holder. One deficiency item in the CR letter (Item #1) will state that DS deficiency items have been sent separately to the DMF Holder. (See Section 13.1.1 CR Letter to Digestive Care, Inc., and Section 13.1.2 Deficiency Letter to (b) (4).)

4. Nonclinical Pharmacology/Toxicology

4.1 Initial Review Cycle

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Tamal Chakraborti dated June 19, 2009, for complete information.

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance⁶, 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 Pertzye clinical development program. However, toxicology studies are needed if the excipients in the Pertzye 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, no new pharmacology or toxicology studies were conducted with Pertzye and no new non-clinical

⁶ 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/6275f1.htm>> April 2006.

studies were submitted in the NDA submission. The non-clinical information provided by the Applicant in the submission was from the published literature for the excipients in the clinical formulation of Pertzye.

Dr. Chakraborti notes that in a FDA communication dated July 11, 2006, the Division recommended that a comprehensive summary with sufficient details of chronic toxicology studies for the excipients would be needed for the NDA. DCI provided a comprehensive summary of the toxicology data available for each excipient used in the formulation of Pertzye. Dr. Chakraborti notes that based on the available toxicology data for each excipient used in the Pertzye 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. Chakraborti concludes that there appears to be no anticipated risks associated with the use of Pertzye at the proposed clinical doses in patients with EPI.

Dr. Chakraborti recommends an Approval action based on the non-clinical review of the information submitted in the NDA. Dr. Chakraborti 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: “Pregnancy Category C: Animal reproduction studies have not been conducted with Pertzye. It is not known whether Pertzye can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pertzye capsules should be given to a pregnant woman only if clearly needed.”
- Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility): Wording in the Carcinogenesis, Mutagenesis and Impairment of Fertility section should be revised to:  (b) (4)

Since Pertzye is not recommended for Approval during this review cycle, the proposed labeling changes will be planned for negotiation with the Applicant should Pertzye receive an Approval action during a subsequent review cycle.

4.2 Current Review Cycle

There were no new nonclinical pharmacology/toxicology data in the resubmission, and no additional review of nonclinical data was performed in the second review cycle.

4.3 Final 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 Initial Review Cycle

The reader is referred to the Clinical Pharmacology Review by Peifan Bai dated June 9, 2009, and the Addendum to the Clinical Pharmacology Review by Peifan Bai dated August 26, 2009, for complete information.

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

In Vivo Intubation Study (Bioavailability Study):

This was an open-label, placebo-controlled, crossover study that evaluated the bioavailability of Pertzze in seven patients with EPI. Five capsules of Pertzze MS-16 or placebo were taken with the Lundh test meal (a liquid test meal containing protein, fat, and sugar); gastric and duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Based on the clinical pharmacology reviewer's calculation after taking into account the lipase activity recovered following placebo, there appears to be only a small amount of % lipase activity (<10%) recovered following Pertzze. The reviewer commented that clogging of catheters might have influenced the outcome of duodenal lipase recoveries. 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.

In Vitro Stability Study (Food Compatibility Study):

The percentages of lipase activities recovered after mixing with applesauce were determined for each of the three ^{(b) (4)} dosage strength formulations. The results are listed below.

Mean (SD) % lipase activities after exposure to applesauce at room temperature are shown in the table below.

Table 3. Mean (SD) % Lipase Activities After Exposure to Applesauce at Room Temperature

	Dosage Strength Formulations		
	MS-4	MS-8	MS-16
Exposure Duration	40 minutes	60 minutes	50 minutes
Lipase activity	90% (3.5%)	91% (3.8%)	93% (3.6%)

(Table above modified from table in Dr. Bai's Clinical Pharmacology Review dated June 9, 2009.)

Upon initial review (see Dr. Bai's Clinical Pharmacology Review dated June 9, 2009), Dr. Bai concluded the following: (a) Based on the above results for individual strengths, the lipase activities recovered after mixing with applesauce were higher than the current standard of at least 90%. (b) Pertzze microspheres, MS-4, MS-8 and MS-16, were stable after exposure to applesauce at room temperature for 40 min, 60 min, and 50 min, respectively. (c) The study results support the use of applesauce as a medium to facilitate ingestion of Pertzze microspheres.

Dr. Bai revised the assessment of the *in vitro* stability study (see Dr. Bai's Addendum to Clinical Pharmacology Review dated August 26, 2009) after the CMC reviewer had identified a product deficiency (see Item #10 of Deficiency Items in Appendix 4) related to measurement of lipase activity. Dr. Bai's final recommendation is for the Applicant to repeat the *in vitro* stability study using the analytical method described in Deficiency Item #10 (i.e., use of a minimum of 5 data points for determination of assay linearity rather than (b) (4) data points) but otherwise the same study design as that submitted.

In the first review cycle, a CR action was the recommendation by the Clinical Pharmacology discipline (see Deficiency Item # 19 in the CR Letter dated August 27, 2009; Appendix 4).

5.2 Current Review Cycle

5.2.1 Clinical Pharmacology

In the current review cycle, the clinical pharmacology reviewer determined that the Applicant's response to address the clinical pharmacology deficiency item (Item #19 in the CR Letter dated August 27, 2009; see Appendix 4) was not acceptable. (See Clinical Pharmacology Review by Jang-Ik Lee dated January 13, 2011.)

The clinical pharmacology reviewer noted that the Applicant addressed the issue of constructing the calibration curve for the lipase assay (CMC Deficiency #10), but did not determine the accuracy and precision of the assay by simultaneously running quality control (QC) samples to check the in-process lipase assay performance. The clinical pharmacology reviewer also pointed out that the study report submitted to demonstrate the *in vitro* stability (food compatibility) of the proposed product when mixed with applesauce is not complete for performance of a sufficient clinical pharmacology review.

The clinical pharmacology reviewer stated that if the applicant wishes to include the proposed labeling language for administration of the product via mixing with applesauce, the applicant would have to submit the following information:

- (a) an adequate assay validation report with the assessment of in-process assay performance; and
- (b) a complete food compatibility study report that would allow for a substantial clinical pharmacology review.

A CR Letter deficiency item will be communicated to DCI from the Clinical Pharmacology discipline (see **Item #8** in Section 13.1.1 of this CDTL Review).

5.2.2 Biopharmaceutics

In response to deficiency item #20 in the CR Letter (see Appendix 4), the applicant developed (b) (4) new MS-8, containing (b) (4) 8,000 USP lipase units, (b) (4)

(b) (4). The applicant also provided dissolution testing data (including methodology and proposed specification) for each of the dosage strength formulations. (See Biopharmaceutics Review by Tien-Mien Chen dated December 9, 2010.)

The Biopharmaceutics Reviewer determined that a biowaiver cannot be granted for the (b) (4) lower dosage strength (b) (4) 8,000 USP lipase unit formulations) for the following reasons:

- (a) The applicant's proposed dissolution methodology is not considered optimal.
- (b) The applicant's proposed specification of $Q=(b) (4)$ at 30 minutes is considered less than ideal.

For (b) (4) dosage strength formulations ((b) (4) MS-8, and MS-16), results for lipase activity (potency) at Month 0 using the USP method differed from the results of dissolution testing methods after 30 minutes.

- USP method (at Month 0): Mean lipase activity (potency) of (b) (4) to (b) (4) was obtained.
- Dissolution testing methods (at Month 0): Mean lipase activity (potency) was (b) (4) to (b) (4) after 30 minutes.

The Biopharmaceutics Reviewer noted that the applicant did not fully justify the loss of lipase activity during dissolution testing.

The Biopharmaceutics Reviewer wishes to communicate the following comments to the Applicant:

1. You responded on 03/31/10 to the Agency's request on 03/22/10 for further exploration and/or explanation for the causes of the loss of the activity during the dissolution testing. You indicated that 1) You already explored various conditions (under study report No. RR-083) and 2) The Agency, in a letter dated 05/07/09, already accepted the sponsor proposed dissolution specifications $Q=(b) (4)$ at 30 min.

The Agency needs more information in order to make a final decision. Based on the results of the study No. RR-083, you selected the fortified intestinal fluid as a medium for the dissolution testing in which the substrates were added to stabilize the pancrelipase, i.e., olive oil for lipase, casein for protease, and starch for amylase (assay method TM-6013).

However, you have not determined in your assay method (TM-6013) if the amount of olive oil added to the fortified intestinal fluid will later affect the determination of lipase activity when titrating the fatty acid liberated from the substrate, olive oil, after being digested by lipase.

Therefore, your proposed $Q=(b) (4)$ at 30 min is not considered fully justified. Please justify for the use of fortified intestinal fluid as a dissolution medium vs. the use of the USP lipase assay method.

2. Please consider conducting dissolution testing using the USP dissolution method, i.e., in the acid stage for 1 hour and then transfer the content to the buffer stage.

3. Provide individual and mean dissolution data (at 10, 20, and 30 min in the buffer stage) and mean dissolution profiles of the (b) (4) proposed strengths.
4. Propose an acceptance criterion for the dissolution of your products.

Although these comments should be addressed prior to resubmission, these are not approvability issues at this time.

5.3 Final Recommendation

Clinical Pharmacology: A Complete Response Action is the recommendation by the Clinical Pharmacology discipline (see Deficiency Item #8 in Section 13.1.1 CR Letter to Digestive Care, Inc.).

Biopharmaceutics: A biowaiver for the (b) (4) lower strengths cannot be granted at this time. Comments were provided that should be communicated to the applicant (see Section 5.2.2 above and Section 13.7 below); although these comments should be addressed prior to resubmission, these are not approvability issues at this time.

6. Clinical Microbiology

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

7. Clinical/Statistical - Efficacy

7.1 Initial Review Cycle

The reader is referred to the original Clinical Review by Marjorie Dannis dated August 27, 2009, and the Statistical Review by Freda Cooner dated July 21, 2009, for complete information.

(b) (4)
The MS-16 formulation has been marketed in the United States from 2004 to approximately the middle of 2010 (see Section 2.2.1) under the name “Pancrecarb.”

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

Clinical Studies

The pivotal study (06-001) and the supportive study (97-001-1B) were reviewed in depth by the Clinical Reviewer. Pertinent features of these studies are summarized in the table below.

Table 4. Selected Pertzze Clinical Studies

Study No.	Design	Product	Primary Endpoint / Objective	No. of Pts	Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo-controlled, two-way crossover	MS-16 and Placebo	Change in CFA	21	8-43	CF
97-001-1B	Randomized, open-label, active-control two-way crossover	MS-8*	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19	12-27	CF

*It should be noted that the formulation of Pertzze MS-8 in this study (submitted in the previous submission) is not the same as the Pertzze MS-8 formulation proposed in the current resubmission. (Table above is modified from table found in Clinical Review by Marjorie Dannis.)

A full listing of Pertzze clinical studies is provided in Appendix 2.

Efficacy Results

Study 06-001

The primary efficacy endpoint in the pivotal study 06-001 was the comparison of percent coefficient of fat absorption (% CFA) to a % CFA on placebo treatment. % CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet. The formula for the % Coefficient of Fat Absorption (CFA) is provided below:

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

In severely affected patients (i.e., patients with a baseline % CFA of $\leq 40\%$), a clinically meaningful change in % CFA is considered to be an increase of $\geq 30\%$. For patients with baseline % CFA $> 40\%$, no accepted change in % CFA has been established. More severely affected patients (i.e., patients with lower baseline % CFAs) are expected to experience larger increases in % CFA with PEP treatment than less severely affected patients (i.e., patients with higher baseline % CFAs).

The pivotal study, 06-001, was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pertzze MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI). Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pertzze MS-16 and placebo. Pertinent features of the study design are summarized in the table below.

Table 5. Pertinent Features of Study Design

Study Days	Period*	Treatment
-14 to -10	Screening Period (4 days)	--
-10 to 0	Dose Stabilization Period (7-10 days)	Pertzye
1 to 2 (home) 3 to 6 (GCRC)	Treatment Period 1 (6-8 days)	Pertzye or Placebo
7 to 10	Washout/Re-stabilization Period (7-10 days)	Pertzye
1 to 2 (home) 3 to 6 (GCRC)	Treatment Period 2 (6-8 days)	Pertzye or Placebo

* The follow-up period includes the end of the study visit (14 days after discharge at the end of Treatment Period 2)

GCRC: General Clinical Research Center

(The table above is modified from a figure and supporting text found in the Clinical Review by Marjorie Dannis.)

Doses in this study were not to exceed a maximum lipase dose of 2500 lipase units/kg/meal, which is in agreement with CFF recommendations (see Appendix 1). The dose for each subject (for the Dose Stabilization Period and Treatment Periods) was selected as follows:

- **Dose Stabilization Period:** During the Dose Stabilization Period, a high-fat diet (approximately 2 gm fat/kg/day) was consumed. The patient's Pertzye MS-16 dose was managed in order to achieve control of pancreatic insufficiency symptoms and to achieve stabilized status according to the clinician's observations and subject's signs and symptoms.
- **Treatment Periods:** The dose chosen during the Dose Stabilization Period was used during the subsequent Treatment Periods.

The results of the study show that 29 patients were enrolled in the study, and 24 patients were randomized. Twenty-one patients completed the study. Three patients discontinued the study after randomization (two for adverse events, and one for a protocol violation).

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

Table 6. Demographics of Study 06-001

	Children < 18 (n=11)	Adults ≥ 18 (n=13)	Overall (n=24)
Age (years)			
Mean (SD)	12 (2.9)	27(7.4)	20(9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

(Table above is taken from the Clinical Review by Marjorie Dannis.)

The mean age overall was 20 years (range 8 to 43 years). In children (≥ 7 to 17 years), the mean age was 12 years. In adults (≥ 18 years), the mean age was 27 years. More males than females were enrolled in both age groups (overall: 18 males, 6 females; children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly Caucasian (92%) which is consistent with the racial/ethnic prevalence of this disease.

The mean CFA for patients receiving Pertzze was 83%; the mean CFA for patients receiving placebo (no treatment) was 46%. The mean change in CFA was 36% ($p < 0.001$; 95% CI [28, 45]). The FDA Statistician confirmed the results and was agreement with the Applicant. The results are summarized in the table below.

Table 7. Comparison of %CFA (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162 ^a	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007 ^a	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317 ^a	25.848, 48.786

^a $P < 0.001$

(Table above is taken from the Clinical Review by Marjorie Dannis; source was listed as 06-001 Study Report.)

A simple t-test for two independent samples or a paired t-test was performed by the Statistical Reviewer; similar results were seen. (See Statistical Review by Freda Cooner.)

The clinical reviewer and statistical reviewer also performed analyses of the primary endpoint in subgroups defined by placebo CFA ($< 40\%$ and $\geq 40\%$). The results (from the Statistical Review) are shown below:

Table 8. Comparison of CFA Stratified by Placebo CFA (%), Completed-Treatment Population) for Study 06-001

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Placebo CFA < 40%				
Overall (n = 9)	76.990	25.298	51.692 ^a	(38.390, 64.994)
Children (n = 5)	73.629	24.871	48.758 ^a	(29.947, 67.570)
Adults (n = 4)	80.350	25.725	54.625 ^a	(35.813, 73.437)
Placebo CFA $\geq 40\%$				
Overall (n = 12)	86.676	61.018	25.658 ^a	(18.008, 33.307)
Children (n = 5)	86.607	62.752	23.855 ^b	(12.075, 35.635)
Adults (n = 7)	86.745	59.284	27.461 ^a	(17.529, 37.293)

^a $P < 0.001$

^b $P = 0.0013$

Source: Reviewer's Table

(Table above is taken from the Statistics Review by Freda Cooner.)

The patients who had a placebo CFA $\geq 40\%$ showed smaller increases in CFA after treatment with Pertzze than patients who had a placebo CFA $< 40\%$. The statistical reviewer noted that using the t-tests, these results did not change.

The statistical reviewer commented that although it can be concluded that there is an overall treatment effect of Pertzze MS-16 on CFA, it is not known whether Pertzze MS-16 would improve CFA for the patients with placebo CFA levels greater than 80% due to lack of data in that subgroup.

Study 97-001-1B

The supportive study, 97-001-1B, was a multicenter, randomized, open-label, active-controlled, two-way crossover study evaluating the efficacy and safety of Pertzze MS-8. It should be noted that the formulation of Pertzze MS-8 in this study (submitted in the previous submission) is not the same as the Pertzze MS-8 formulation proposed in the current resubmission.

This study, in 19 patients with a confirmed diagnosis of CF and EPI, was designed to compare measures of fat malabsorption before (while on usual PEP treatment) and after oral administration of Pertzze MS-8 at an approximately 50% reduced lipase dose.

Dosage: The dosage of Pertzze MS-8, the test pancreatic enzyme, and the reference pancreatic enzymes [Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18, and MT-20 (Axcen/Scandipharm)] were adjusted to approximately 50% of each patient's routine lipase dose requirement, but not lower than approximately 1,800 USP units of lipase per gram of fat intake per day.

Overview of Study Design:

- Screening Visit: At the time of the screening visit, all patients had received pancreatic enzyme therapy in the form of Creon®, Pancrease®, or Ultrase®. After determination of the current lipase dose, the existing enzyme therapy dose was reduced by approximately 50%, but no lower than approximately 1800 units of lipase per gram of fat intake per day. Only those patients with a CFA < 85% during the initial approximately 50% reduced enzyme dose were randomly assigned in the two crossover treatment periods.
- Treatment Periods: The study was carried out during two consecutive seven-day treatment periods in patients with CF. These reduced lipase doses were maintained throughout the study during each seven day treatment arm of the study. Following the first stool collection, the patients were instructed to collect stools for an additional three days on their reduced lipase dose.

The results of the study sho

(b) (4)

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

Table 9. Summary of Baseline Demographics (ITT Population)

	Cincinnati site (n = 8)	Indianapolis site (n = 11)	Overall ^a (n = 19)
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6

^a The results are in agreement with those from the Applicant.

(Table above is taken from the Clinical Review by Marjorie Dannis.)

The mean age overall was 18 years (range 12 to 28 years). Approximately equal proportions of males and females were enrolled. The patients were mostly Caucasian (95%) which is consistent with the racial/ethnic prevalence of this disease.

The ITT results (see table below) (b) (4)

As per the Sponsor’s analysis, this change in CFA was statistically significant (see table below).

Table 10. Efficacy Results Study 97-001-1B

	Pertzye MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19)			
CFA (%)			(b) (4)
PP Population (n=18)			
CFA (%)			

* One patient (011) at the Indianapolis site was non-compliant to the protocol specified diet and was identified by the sponsor as a major protocol violation.

Table above is taken from the Clinical Review by Marjorie Dannis; source was listed as Statistical Reviewer’s Table.

The statistical reviewer commented: “Due to the fact that this study was open-label, had no washout period between two crossover treatment periods, used repeated treatment assessments, and had changes in the analysis plan, the results cannot reliably support an efficacy claim.”

Dosage Strength Formulations

Comparability of the (b) (4) formulations (b) (4) MS-8, and MS-16) relative to one another was not shown by the information provided in the original NDA submission. (b) (4)

The clinical and statistical reviewers each noted that although the pivotal study (06-001) demonstrated a treatment effect with the MS-16 formulation, the other controlled study (97-001-1B) lacked statistical rigor to support any efficacy claims of the MS-8 formulation, and there were no other controlled clinical studies submitted in support of demonstration of efficacy of MS-8 (b)(4). Thus, the reviewers were unable to determine the efficacy of the (b)(4) MS-8 formulations.

In the first review cycle, the Clinical Reviewer recommended that if an approval action was taken, only the MS-16 dosage strength formulation should be allowed for approval as the clinical data submitted in the original NDA submission were adequate to label the MS-16 formulation for patients with EPI; the Statistical Reviewer agreed with this recommendation.

For the other dosage strength formulations ((b)(4) MS-8), the Clinical Reviewer recommended the following:

(b)(4)

The above were communicated to the Applicant in the CR letter (see Item #20 in CR Letter in Appendix 4).

7.2 Current Review Cycle

No additional efficacy data was submitted in the current review cycle.

In response to the clinical deficiency item in the CR Letter (Item #20; see Appendix 4), (b)(4)

(b)(4) The Applicant provided process validation, release and stability data, and dissolution data for the new (b)(4) MS-8 capsules (see Sections 3.2 and 5.2).

7.3 Final 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 Marjorie Dannis dated August 27, 2009 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.^{7,8,9} (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.

⁷ 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.

⁸ 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.

⁹ 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.^{10,11} (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 First Review Cycle

The reader is referred to the original Clinical Review by Marjorie Dannis dated August 27, 2009 for complete information.

Exposure

The safety population includes 262 subjects exposed to Pertzze covering a treatment period ranging from seven days to more than two years. (The safety population was defined as any subject who received at least one dose of Pertzze.)

The safety of Pertzze was evaluated in ten clinical studies. Studies 06-001 and 97-001B have been described in detail in Section 7 of this review; the other eight studies are described in Appendix 2.

¹⁰ Antiviral Drugs Advisory Committee (December 2, 2008);
<<http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs>>

¹¹ Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

The overall exposure is summarized by study in the table below.

Table 11. Mean Lipase Doses and Duration of Dosing in Clinical Studies

Study No.	Duration of PANCRECARB® Treatment	Lipase Dose Measure	PANCRECARB® Mean Lipase Units		Comparator Mean Lipase Units
06-001			PANCRECARB® MS-16		Placebo
	7 days	Units/kg/meal	1,565 (SD 563)		n/a
97-001-1B			PANCRECARB® MS-8		Usual Enzyme*
	7 days	Units/kg/meal	1,158 (SD 429)		1,145 (SD 448)
		Units/kg/day	4,237 (SD 1,873) ^a		4,189 (SD 1,913)
091897			PANCRECARB® MS-8		Initial History
	Up to 2 years	Units/kg/day	4,576 (SD 3,071)		9,898 (SD 12,004)
97-001-2			PANCRECARB® MS-8		Creon® 10 or 20
	7 days	Units/kg/day	8,682 (SD 3,369)		16,519 (SD 7,207)
071503			PANCRECARB® MS-16		Usual Enzyme*
	14 days	Units/kg/day	5,430 (SE 510)		7,838 (SE 637)
2001-180			PANCRECARB® MS-4		Viokase® powder ^b
	30 days	Units/kg/day	4,490 (SE 1,251)		9,128 (SE 1,251)
020296			PANCRECARB® MS-8 ^c		Cotazym® ECS-8
	14 days	Units/kg/day	6,071 (SD 1,072)		6,810 (SD 1,860)
111395			PANCRECARB® MS-8 ^c		Usual Enzyme**
	14 days (per phase)	Units/day	Phase 2 273,143 (SD 153,014)	Phase 3 192,503 (SD 87,907)	Phase 1 323,200 (SD 153,823)
		Units/kg/day ^d	5,811	4,096	6,875
092100			PANCRECARB® MS-8		Placebo
	7 days	Capsules/Day	6.9 (SD 2.8)		n/a

*Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcen/Scandipharm)

**Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-16 (Ortho/McNeil); Ultrase® MT-20 (Axcen/Scandipharm); Cotazym® ECS-8 (Organon)

^a Units/kg/day represent an approximate 48% reduction from the patients' usual lipase dose of 8,760 units, calculated from the average of the range of the number of capsules per day at study entry.

^b Viokase® is a registered trademark of Axcen/Scandipharm.

^c A previous formulation (b) (4) PANCRECARB® (pancrelipase) MS-8 drug product was used in these studies.

^d Units/kg/day estimated using a mean body weight of 47kg.

n/a = not applicable

(Table above is taken from the Clinical Review by Marjorie Dannis; source is listed as the Applicant's submission.)

Postmarketing Experience: The manufacturer does not have specific data on the number of patients treated with Pertzze formerly marketed as "Pancrecarb." However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b) (4) Pertzze capsules were shipped to wholesalers. If the usual range of daily intake of Pertzze is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pertzze on an annual basis. It should be noted that the formerly marketed MS-16 dosage strength formulation is the same as (b) (4)

(b) (4) the TBMP, but the formerly marketed (b) (4) MS-8 formulations differ from the TBMP formulations (see Section 3).

Safety Findings

Deaths: Four deaths were recorded during the 2-year long term (091897) study period; none were attributed to the use of Pertzze MS-8 (see Clinical Review). No other deaths were reported during any other study with Pertzze.

SAEs: Three Pertzze treated patients experienced four AEs (CF exacerbation and sinusitis in first patient, MVA in second patient, CF in third patient); each of these was considered serious by the study investigator(s). None of the SAEs were considered related to treatment (see Clinical Review). There were two additional hospitalizations (for exacerbation of CF) that were SAEs but not initially reported as such; these events were not considered to be related to enzyme treatment.

Dropouts and/or Discontinuations: Overall, 22 patients (8%) from the total safety population of 262 discontinued for reasons attributed to AE(s); 18 of those 22 were receiving Pertzze. The long-term study (091897) contributed 13 of the 18 Pertzze patients who discontinued due to AE(s). The majority of the AEs were gastrointestinal in nature. The Applicant reported that an additional seven patients discontinued Study 091897 for reasons noted to be due to AE(s) on the CRF clinical summary page, but due to insufficient information, these events were not included in the ISS AE database. The clinical reviewer examined the reports for each of these seven patients, and noted that each of the discontinuations was gastrointestinal in nature (see Clinical Review).

Hypersensitivity Reactions: Two cases of hypersensitivity reactions were reported:

- In Study 06-001, a 17-year-old female experienced a mild rash during treatment phase 2 (Pertzze MS-16) which was considered unrelated to study medication, and which resolved with concomitant medication.
- In Study 97-001B, a 17-year-old male experienced a moderate intensity rash during treatment phase 2 (Pertzze MS-8) which was considered possibly related to study medication. No action was taken and the event resolved completely.

Common AEs: Of the 262 patients treated with Pertzze that were enrolled in a total of 9 clinical studies, 77 (29%) experienced 148 AEs. Of these, 36 (14%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. The most commonly reported AE (>5% incidence) in the Pertzze treated safety group was abdominal pain, with 14 events reported, 11 of which were considered related to treatment. There were 7 reports of severe abdominal pain, 6 of which were considered related to treatment. Other AEs reported for patients treated with Pertzze included upper abdominal pain and headache (n=8 each), diarrhea and flatulence (n=7 each), abdominal distension and frequent bowel movements (n=6 each).

Postmarketing Experience: Pertzze capsules were introduced onto the US market by Digestive Care, Inc. in 1995 (marketed under the name “Pancrecarb”) as a physician prescribed pancreatic enzyme replacement therapy. Annual Drug Product Reviews have

been prepared since 2002. Over this period of time, only two product complaints relating to an adverse drug reaction have been reported. A case of Distal Intestinal Obstructive Syndrome (DIOS) was reported that was determined to be congenital and not considered by the physician to be related to treatment with Pertzze, and one case of allergic reaction (itching and red, blotchy rash on face) in a patient with a history of allergy to another pancrelipase product. It should be noted that the formerly marketed MS-16 dosage strength formulation is the same as (b) (4) the TBMP, but the formerly marketed (b) (4) MS-8 formulations differ from the TBMP formulations (see Section 3).

Conclusion: The Clinical Reviewer concluded that the AE profile of Pertzze as described in the individual studies and in the pooled analysis 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 Current Review Cycle

The clinical reviewer stated in a memo dated January 14, 2011, that since the time of the 4-month safety update (March 17, 2009; reviewed with the original submission), only one additional patient was enrolled in a clinical study and that patient completed the study with no adverse events reported. This was re-affirmed by the applicant in a statement dated September 27, 2010. Thus, the clinical reviewer's conclusions have not changed from the conclusions stated in the original review dated August 27, 2009.

8.3 Final Recommendation

The Clinical Reviewer recommended that the Risk Evaluation and Mitigation Strategy (REMS) be required as part of approval should Pertzze receive an Approval action during a subsequent review cycle. 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 13.1 Recommended Regulatory Action, and 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 not presented to the Pediatric Research Committee (PeRC) during either the first review cycle or the current review cycle because Pertzze was not recommended for

Approval during either of the review cycles. Presentation to PeRC may occur should Pertzze receive an Approval action during a subsequent review cycle.

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. Pertzze is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

The reader is referred to the DSI Review by Roy Blay, dated June 26, 2009 for complete information.

DSI inspections of two clinical sites of Study 06-001 were performed; these were Site 007 (Dr. Strausbaugh; Cleveland, Ohio; n=6) and Site 191 (Dr. Ahrens; Iowa City, Iowa; n=5). These sites were selected by the Division because each of these sites had large percentages of the overall study population; in addition, Site 007 had the highest mean change in the coefficient of fat absorption (%CFA) among study sites. The DSI Inspector commented that for each of the sites review of the records revealed no significant discrepancies/regulatory violations.

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

11.3 Drug Shortage

Currently, Creon, Zenpep, and Pancreaze are the only PEPs that are available on the market that have undergone the NDA review process. Other PEPs that have not undergone the NDA review process can no longer be marketed effective April 28, 2010 (see Section 2.2.1).

Discussions took place with the manufacturers of Creon, Zenpep, and Pancreaze 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. Based on the information obtained from each of the calls, it appears that there are enough PEPs on the market to meet the needs of patients. Thus, even with a Complete Response action for Pertzze, a drug shortage does not appear to be likely.

11.4 Facilities Inspection

During recent inspections of the Digestive Care, Inc. (DCI) manufacturing facility, (b) (4) manufacturing facility, and (b) (4) (contract testing laboratory for (b) (4) the field investigator conveyed deficiencies to the representative of the facilities; based on the Establishment Evaluation System (EES) report, there are “Withhold” recommendations from the Office of Compliance for DCI, (b) (4), and (b) (4). Satisfactory resolution of these deficiencies is required before this application may be approved. The Office of Compliance issued (b) (4). (See also Section 3.2.5.)

12. Labeling

12.1 Proprietary name

Initial Review Cycle:

A review of the trade name “Pancrecarb” was performed by Melina Griffis in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Tradename Review dated March 19, 2009). DMEPA objects to the use of the proprietary name, Pancrecarb, for this product. The results of the Proprietary Name Risk Assessment found the proposed name, Pancrecarb, (b) (4)

A label and labeling review was also performed by Melina Griffis in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated May 8, 2009). Using Failure Mode and Effects Analysis and lessons learned from post-marketing experience with the pancrelipase products, DMEPA evaluated the container labels, carton labeling and insert labeling. DMEPA’s findings indicate that the presentation of information in the labels and labeling (b) (4). Detailed reasons and recommendations are provided in the DMEPA Label and Labeling Review dated May 8, 2009.

Current Review Cycle:

The proprietary name “Pertzze” was deemed acceptable shortly before the start of the current review cycle (see Proprietary Name Request Conditionally Acceptable Letter dated June 11, 2010).

A label and labeling review and a proprietary name review were performed by Irene Chan in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated June 23, 2010 and DMEPA Proprietary Name Review dated June 4, 2010). In addition to a Failure Mode and Effect Analysis, an Adverse Event Reporting System (AERS) Database search was conducted; note that the product had been marketed under the name “Pancrecarb” prior to April 28, 2010 (see Section 2.2.1). The DMEPA reviewer noted that the AERS search conducted on March 18, 2010, yielded no relevant cases. [The MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” were used as search criteria for Reactions. The search criteria used for Products was verbatim substance search “Pancrec%”.] The Failure Mode and Effect Analysis determined that Pertzze is not vulnerable to name confusion that can lead to medication errors.

Final Recommendation:

The proprietary name “Pertzze” was deemed acceptable, but will be re-reviewed should the NDA receive an Approval Action during a subsequent review cycle. As per the Proprietary Name Request Conditionally Acceptable Letter (dated June 11, 2010), the proposed proprietary name Pertzze will be re-reviewed 90 days prior to the approval of the NDA.

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

Initial Review Cycle: The Division of Drug Marketing, Advertising and Communications (DDMAC) found the proposed proprietary name “Pancrecarb” misleading from a promotional perspective. This is documented in the Proprietary Name Review by Melina Griffis dated March 19, 2009.

Current Review Cycle: DDMAC had no concerns regarding the proposed proprietary name “Pertzze” from a promotional perspective, and did not offer any additional comments relating to the proposed name. This is documented in the Proprietary Name Review by Irene Chan dated June 4, 2010.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

Since Pertzze is not recommended for Approval during this review cycle, labeling changes (to Physician Labeling, Medication Guide, and Carton and Container Labeling) will be planned for negotiation with the Applicant should Pertzze receive an Approval action during a subsequent review cycle.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The Primary and Secondary CMC Reviewers recommend this NDA for a CR action because they identified a number of deficiency items in the application. These included drug product deficiencies in release testing, stability testing, process validation, acceptance criteria, and reference standards. In addition, drug substance deficiencies mostly related to microbial limits specification, microbiological testing and monitoring, and a release testing procedure that monitors for the presence of *Bacillus cereus* diarrheal enterotoxin were communicated in a separate letter to the DMF Holder, (b) (4) (DMF (b) (4)).

The Clinical Pharmacology Reviewer recommended this NDA for a CR action because of deficiencies in the methods used for assay validation and in the reporting of the food compatibility study results.

The Microbiology Reviewer concluded that the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) must be adequately addressed before the NDA can be recommended for approval.

GMP deficiencies noted in a recent inspection of DCI, in a recent inspection of (b) (4), and in a recent inspection of (b) (4) (contract testing laboratory for (b) (4)) resulted in Withhold recommendations from the Office of Compliance for DCI, (b) (4) in addition, (b) (4) from the Office of Compliance on (b) (4).

The Nonclinical Pharmacology/Toxicology Reviewer and the Clinical Reviewer recommended this NDA for approval. In addition, the Clinical Reviewer recommended that the Risk Evaluation and Mitigation Strategy (REMS) be required as part of approval should Pertzye receive an Approval action during a subsequent review cycle.

13.1.1 CR Letter to Digestive Care, Inc. (NDA 22-175)

PRODUCT QUALITY

1. (b) (4) DMF (b) (4) has been reviewed in support of NDA 022175 and found to contain deficiencies. A letter dated October 27, 2010, was sent to (b) (4) listing several deficiencies regarding the drug substance manufacturing process. The Agency conveyed additional information requests at a face-to-face meeting held on November 15, 2010, with representatives from (b) (4). (b) (4) should address all deficiencies by directly submitting information to their DMF, or, if the information was previously submitted, then by specific reference to the appropriate submissions. Please

notify us when (b) (4) has submitted the requested information. Satisfactory resolution of the deficiencies identified is required before this application may be approved.

2. You have provided retrospective validation reports for the Pertzeye drug product manufacturing process. Given the complexity of protein products, a prospective process validation should be conducted, to demonstrate your ability to consistently manufacture a product that meets the expected quality standards. Please provide prospective process validation reports with all relevant supporting data to demonstrate that your process is adequately controlled.
3. In regard to your release and stability acceptance criteria, we have the following comments:
 - a. You did not establish an upper limit for the acceptance criteria for the protease and amylase potency assays for release and stability testing. Please establish and justify release and stability acceptance ranges for amylase and protease.
 - b. You have established a lipase stability acceptance range of (b) (4) activity, which is significantly different from the acceptance range ((b) (4) activity) you have established for lot release. The (b) (4) acceptance range is not adequately justified by the data provided in the application and it is unclear how it relates to your clinical experience. Please revise the lipase stability acceptance criterion and provide comments on the following:
 - i. The lipase activity result you have obtained for lot PC-6K09B is significantly different from the results you have obtained on the two other lots used to support the acceptance criteria. Additional lots may need to be analyzed to establish an accurate acceptance criterion for lipase activity during storage of the MS-16 drug product.
 - ii. From the data you have provided, it appears that lipase activity trends toward (b) (4) during storage of the MS-16 drug product. You have not provided information in the application to address the fluctuations in lipase activity during storage of the MS-16 drug product.
4. You are requesting a (b) (4) expiry for the (b) (4) MS-8 drug products. However, you have submitted only nine months of real-time stability data in the application. Expiration dating of protein products is based on real-time, real temperature stability data. Please provide real-time stability data that support your requested expiry dating.
5. You are proposing a qualification program for your drug substance reference standard that includes release testing assays. The acceptance criteria you have established for the qualification program are the same acceptance criteria you are using for release testing. Use of the release acceptance criteria could potentially allow for product characteristics in the new reference standard to be out of trend with the desired or expected product characteristics, thereby introducing drift into the product over time. Please update your reference standard qualification program, as follows:

- a. Your acceptance criteria should be (b) (4) the release acceptance criteria and should be based on manufacturing history and clinical experience.
 - b. Establish upper limits for the protease and amylase specifications.
 - c. Incorporate the RP-HPLC assay in your testing strategy.
6. Your annual stability program for the drug product provides for one lot of material to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions may not be adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. Please incorporate accelerated and/or stressed stability studies in your annual stability program for the drug product.
7. You have provided development and validation studies in support of a new RP-HPLC assay to be performed for release and stability testing of Pertzze. However, it is not clear whether the assay has been implemented. Please provide available release and stability data that include the RP-HPLC assay. Furthermore, please address or provide information for the following items:
- a. You have provided acceptance criteria for six enzyme peaks and for impurities peaks. However, you have not established acceptance criteria for new peaks or for minor peaks that are not included in your acceptance criteria. Furthermore, acceptance criteria should be established for all measurable peaks.
 - b. You have established stability acceptance criteria based on the results obtained on two 30-month old lots. These acceptance criteria would allow for significant decreases in enzyme content, and are not adequately justified. Please revise and scientifically justify your stability acceptance criteria for the RP-HPLC assay.
 - c. In your validation studies you have not evaluated recovery of the samples after chromatography. Additionally, there are no studies that evaluate the lifetime and performance of the chromatography column. Please provide information on sample recovery and validation studies supporting column performance and reuse.
 - d. You have not submitted the method description for the assay conducted at Digestive Care, Inc. (DCI). Please provide the DCI method description and Standard Operating Procedure.
 - e. We have the following comments regarding the (b) (4) method:

- i. You are using a purified elastase standard curve to determine the quantity of the enzymes you have selected to report. However, you have not included a drug product reference standard, to be run along with the samples. The reference standard will ensure that the chromatographic profile of the sample is consistent and that no new peaks appear. Please include a reference standard to be run in each assay.
- ii. You have provided information on how to calculate quantities of the enzymes you have selected to report. However, there is no description of how the impurity levels should be quantified. Please update your method to include a description of the procedures you will use to quantify impurity levels.
- iii. In your method, you state that samples and (b) (4) are stable for (b) (4). However, the study you have conducted to evaluate sample stability was carried out for two days, and no study was conducted to evaluate the stability of the (b) (4). Please provide the results of studies that demonstrate that samples and (b) (4) are stable for (b) (4), or revise your method based on the supporting data you currently have.

CLINICAL PHARMACOLOGY

8. The validation reports for the lipase (TMV-047) and protease (TMV-043) assay methods submitted on February 15, 2010, are not acceptable to fulfill Clinical Pharmacology Deficiency # 19 in the complete response letter dated August 27, 2009. Furthermore, the applesauce compatibility study report (RR-166) is not considered complete.
 - a. We recommend that you evaluate in-process assay performance during actual study sample runs by simultaneously running quality control samples. For additional information regarding the preparation of adequate assay performance reports, we refer you to Section C. Application to Routine Drug Analysis (page 17) in FDA's Guidance for Industry: Bioanalytical Method Validation, located at: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>).
 - b. We also recommend that you submit a comprehensive applesauce compatibility report so that we may complete our clinical pharmacology review. For example, the methods section needs to include information in sufficient detail such that an independent laboratory could reproduce your results. At least 3 product batches need to be tested for each product strength.

FACILITY INSPECTIONS

During an inspection of a manufacturing facility referenced in this application, (b) (4) conducted between (b) (4) and (b) (4), the FDA investigator conveyed deficiencies to a representative of the facility. (b) (4) response dated (b) (4), addressing the deficiencies listed on FDA form 483 dated

(b) (4) was not adequate. Satisfactory resolution of these deficiencies is required before this application may be approved.

During a recent inspection of the Digestive Care, Inc. manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated March 19, 2009, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Pertzze (pancrelipase) Delayed-Release Capsules to ensure that the benefits of the drug outweigh the known risk of fibrosing colonopathy associated with higher doses of pancreatic enzyme products (PEPs), and the theoretical risk of transmission of viral disease to patients.

We acknowledge the submission of your proposed REMS on July 31, 2009, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS “PROPOSED REMS-AMENDMENT for NDA 022175.”

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

13.1.2 Deficiency Letter to (b) (4) (DMF (b) (4))

The deficiencies below were sent to (b) (4) (DMF (b) (4)) in a letter dated October 27, 2010.

1. Provide a list of all contract laboratories that will be used in support of manufacturing your products. Include the specific tests that will be performed by each laboratory, the company name, and address where testing is to be conducted. For each laboratory provide a point of contact including name, phone, fax, and email address.
2. For any contract laboratory used in support of manufacturing your products, provide a copy of the quality agreement between the contract laboratory and the associated manufacturing site.
3. For NDA 022222, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
4. For NDA 022542, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.

5. For NDA 022175, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
6. The establishment inspection report indicates that you have implemented a change in the drug substance intermediate storage container, from (b) (4) white drums to (b) (4) blue drums. Provide the results of studies conducted to demonstrate that the change in storage container will not adversely impact product quality. Specifically, submit the following information:
 - a. Extractable/leachable studies and risk analysis performed on the HDPE storage container.
 - b. Evaluation of the quality of pancrelipase manufactured using the (b) (4) containers.
 - c. Available stability data on lots of pancrelipase manufactured using the (b) (4) containers.
 - d. Since your process provides for re-use of the drug substance intermediate storage container, provide the results of validation studies performed to support re-use of the (b) (4) container.

Additionally, review your manufacturing process and verify that the information provided in the DMF accurately reflects your current manufacturing process for drug substances 1206, 1208, 1252, and 1286. If changes were incorporated in the process, provide a list of changes and all relevant data to demonstrate that the changes do not adversely impact product quality.

7. Provide an update on efforts to reduce the bioburden on incoming pancreas glands.
8. Provide the microbial limits specification for pancreatin drug substance manufactured using the 1206 and 1208 processes.
9. Update the manufacturing procedures for the 1208 and 1206 processes with clearly defined time limits for each manufacturing step and the points at which samples for microbiological testing will be collected.
10. Update the information regarding microbiological monitoring of the (b) (4) with the following:
 - a. The bioburden alert and action levels from the (b) (4) manufactured using the 1206 and 1208 manufacturing processes.
 - b. A commitment to test the bioburden of the (b) (4) from each drum immediately prior to (b) (4)
11. Reaffirm your actions provided previously in the May 4, 2010 amendment to DMF (b) (4) (response to item 2) regarding exceeded microbiological alert and action levels.
12. Provide a commitment to clean all processing equipment between individual batches.
13. Section 3.2.S.7.1.2.4.1 in the August 12, 2010 submission lists the total aerobic microbial count (TAMC) limits for stability batches of drug substance at (b) (4) (1206) and (b) (4) (1252). The microbial limits for all pancrelipase stability batches

should be at or below the levels established for release testing. Provide updated stability batch acceptance criteria for each of the pancreatin products.

14. As a condition of NDA approval:
 - a. Develop and implement a release test procedure that monitors for the presence of *Bacillus cereus* diarrheal enterotoxin in pancrelipase samples.
 - b. Provide a commitment to test each batch of drug substance for *Bacillus cereus* diarrheal enterotoxin prior to release.

13.2 Risk Benefit Assessment

The benefit characteristics appear similar to those of already marketed PEPs for treatment of EPI. The outstanding risk issues with this application are concerns about the ability of the drug substance manufacturer to adequately ensure the microbial quality of the drug substance (see Items #7 to #14 in Section 13.1.2 of this review), and concerns about adverse effects on product quality from a change in the drug substance intermediate storage container (see Item #6 in Section 13.1.2 of this review).

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

See Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since Pertzze is not recommended for Approval during this review cycle, recommendations for postmarketing required pediatric studies will be made should Pertzze receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

As described in our letter dated August 27, 2009, we have determined that if this application is approved, you will be required to conduct postmarketing studies for Pertzze (pancrelipase) Delayed-Release Capsules to assess a known serious risk of fibrosing colonopathy and an unexpected serious risk of transmission of viral disease to patients taking Pertzze (pancrelipase) Delayed-Release Capsules.

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

Any additional specific details for these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete one or both of these studies prior to re-submitting your application, you may include the final report(s) and relevant data sets in your Complete Response submission to facilitate review of the information.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

Since Pertzze is not recommended for Approval during this review cycle, postmarketing commitments will be planned for negotiation with the Applicant should Pertzze receive an Approval action during a subsequent review cycle.

13.7 Recommended Comments to Applicant

The additional comments below should be communicated to the applicant. Although these comments are not approvability issues at this time, the applicant should address these in their resubmission.

1. You responded on March 31, 2010 to the Agency's request on March 22, 2010, for further exploration and/or explanation of the causes for the loss of lipase activity during the dissolution testing. You indicated that 1) you have already explored various conditions (under Study No. RR-083) and 2) the Agency, in a letter dated May 7, 2009, had already accepted your proposed dissolution specifications $Q = \text{[redacted]}^{(b)(4)}$ at 30 min.

The Agency needs more information in order to make a final decision regarding this issue. Based on the results of Study No. RR-083, you selected fortified intestinal fluid as a medium for dissolution testing in which the substrates were added to stabilize the pancrelipase, i.e., olive oil for lipase, casein for protease, and starch for amylase (assay method TM-6013).

However, you have not determined in your assay method (TM-6013) if the amount of olive oil added to the fortified intestinal fluid will later affect the determination of lipase activity when titrating the fatty acid liberated from the substrate, olive oil, after being digested by lipase.

Therefore, your proposed $Q = \text{(b) (4)}$ at 30 min is not considered fully justified. Please justify the use of fortified intestinal fluid as a dissolution medium vs. the use of the USP lipase assay method.

2. Please consider conducting dissolution testing using the USP dissolution method, i.e., in the acid stage for 1 hour and then transferring the contents to the buffer stage.
3. Provide individual and mean dissolution data (at 10, 20, and 30 min in the buffer stage) and mean dissolution profiles of the (b) (4) proposed strengths.
4. Propose an acceptance criterion for the dissolution of your products.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995¹²) 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. 2002¹³ 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. 1997¹⁴ 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

¹² 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.

¹³ 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.

¹⁴ 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: List of Pertzye Clinical Studies

Table 12. Complete List of Pertzye Clinical Studies

Study No.	Design	Product	Primary Endpoint / Objective	No. of Pts	Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo-controlled, two-way crossover	MS-16 and Placebo	Change in CFA	21	8-43	CF
97-001-1B	Randomized, open-label, active-control two-way crossover	MS-8	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19	12-27	CF
97-001-2	Nonrandomized, open-label, active-control one-way crossover	MS-8	Change in CFA/between usual dose and 50% reduced lipase dose Pertzye	6	4-17	CF
2001-180	Nonrandomized, open-label, active-control one-way crossover	MS-4	Compare CFA decrease lipase dose by 50%; given by G-tube	6	5-15	CF
092100	Double-blind, randomized, placebo-controlled, two-way crossover	MS-8 and Placebo	Reduction in the frequency of diarrhea	13 [†]	28-55	HIV+ patients [#]
092206	Bioavailability, open-label, placebo-controlled, bioavailability	MS-16 and Placebo Single dose	Demonstrate the intestinal bioavailability of lipase, amylase, and protease from Pertzye MS-16	10	36-79	Documented Chronic Pancreatitis*
091897	Nonrandomized, uncontrolled, open-label	MS-8	Weight gain	106	2-42	CF
071503	Nonrandomized, open-label, active-control one-way crossover	MS-16	Difference in mean doses/Determine lowest effective lipase dose	18	12-41	CF
020296 (older formulation [†])	Double-blind, randomized, active-controlled, 2-way crossover	MS-8 (b)(4)	Differences in CFA between the two treatment periods	22	8-41	CF
111395 (older formulation [†])	Non-randomized, open-label, active-controlled, 1-way crossover	MS-8 (b)(4)	Differences in CFA between the two treatment periods	10	8-16	CF

*Alcohol-induced chronic pancreatitis or CF

[#]Experiencing HAART induced diarrhea that is successfully managed by pancrelipase therapy.

[†]11 patients completed the study.

[‡] Two clinical studies from 1996 (Studies 020296 and 111395) used an older formulation (b)(4)
(Table above is modified from table found in original Clinical Review by Marjorie Dannis.)

2 pages of Appendix 3 have been Withheld in Full immediately following this page as a duplicate copy of Consult Memo dated June 5, 2009 which can be found in Other Reviews of NDA 22222

APPENDIX 4: NDA Deficiency Items – First Action

Deficiencies from the CR Letter (NDA 22-175) dated August 27, 2009 are provided below:

3 pages of Appendix 4 have been Withheld in Full immediately following this page as a duplicate copy of the Other Action letter dated 08/27/2009 which can be found in this approval package



APPENDIX 5: DS Deficiency Items – First Action

Deficiencies in Drug Substance (from DMF Deficiency Letter sent to (b) (4) dated August 28, 2009; Master File (b) (4)):

1. Provide the following information regarding the handling and testing of the intact pancreas glands prior to (b) (4)
 - a) Are the glands washed or processed in any way prior to (b) (4)?
 - b) Are microbiological acceptance criteria in place for the pancreas glands?
2. Section 3.2.S.2.1.2.2 of DMF (b) (4) states that the maximum length of the pancreatin/pancrelipase manufacturing process is (b) (4). Please provide the following information regarding the manufacturing process:
 - a) A justification for this extended processing time
 - b) The maximum storage time and storage temperature of the (b) (4) stored in (b) (4) drums
 - c) Data showing that the (b) (4) stored in the (b) (4) drums does not support microbial growth
3. Please provide the results of the forced degradation studies used to evaluate the suitability of the RP-HPLC assay for stability testing.
4. Please define the amount of raw material used in the manufacturing of drug substance 1206.
5. Please provide a scientific justification as to why the acceptance criterion for (b) (4) is different between drug substances 1206 and 1208.
6. On page 47 of the 2008 annual update (Section 3.2.S.2), you refer to “finished product”. Please clarify what you define as “finished product”.
7. You have not submitted information on drug substance manufactured with the 1206 process. Please provide the following:
 - a) In-process control testing acceptance criteria for lipase activity and microbial limits (b) (4).
 - b) Acceptance range of yield for each critical manufacturing step with information supporting this range.

- c) Operating and performance parameters for critical steps in the manufacture of 1206 and 1208 drug substances.
 - d) Process validation data for 1206 drug substance.
 - e) (b) (4) enzyme activity characterization studies on drug substance 1206 using olive oil as substrate.
8. In your release testing program of drug substances 1206 and 1208, establish acceptance criteria with upper and lower limits for peak areas for all peaks identified by RP-HPLC.
9. In regards to your release and stability programs for drug substance 1206, we have the following comments:
 - a. Establish acceptance criteria for enzymatic activities with upper and lower limits.
 - b. Include additional quantitative assays, not limited to RP-HPLC, to measure product-related substances and impurities.
10. Provide trended stability data of drug substance 1206.
11. We recommend you expand your olive oil testing program to include monitoring for critical olive oil attributes. Please establish acceptance criteria for critical olive oil components (i.e. oleic acid), based on your historical testing results.
12. Please submit the following enzyme method validation study protocols and reports to the DMF: Lipase (b) (4), Protease (b) (4), and Amylase (b) (4).
13. Please identify an expiry or hold time for 1206 and 1208 drug substances before (b) (4) and provide data supporting your proposal.
14. Your testing program for the 1206 (b) (4) is not adequate. Specifically, we have the following comments:
 - a. Please update the testing protocol to include additional tests, such as HPLC, for measurement of impurities.
 - b. Please revise your acceptance criteria for enzyme activity by establishing upper and lower limits. Established acceptance criteria for all the tests performed pertaining to enzyme activity.
 - c. Please provide a clear description of the LOD method and clarify the unit of measurement.

15. Due to the past inconsistencies of the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
16. Please submit the results of the study conducted to demonstrate the equivalency of the (b) (4).
17. You have not provided a detailed description of the sanitizing/cleaning procedures in place to help prevent viral cross-contamination between different batches of drug substance. Please provide a detailed description of your sanitization program and provide an assessment of the ability of cleaning agents currently used in the facility to inactivate diverse viral agents. If the cleaning agents are inadequate, provide a plan to implement appropriate cleaning agents to ensure inactivation of viral agents to prevent cross contamination between different batches of drug substance. Include a description of any additional procedures in place when dealing with equipment contamination with a virus that possess a risk to product quality.
18. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1) to establish lot release specifications for the drug substance.
19. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release.
20. Please provide a calculation of estimated enveloped and non enveloped viruses per dose of API (b) (4) based on the limit of detection of the Q-PCR assays from sufficient batches of the drug substance and discuss how your proposal provides an appropriate level of control for enveloped and non enveloped viruses given the current estimate of the manufacturing process's ability to inactivate these viruses.
21. The sensitivity of the qPCR assays used to monitor for EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reovirus), Rota (Rota Virus), VSV (Vesicular Stomatitis Virus), and PTV (Porcine Teschovirus) viruses is in the range of (b) (4) genomes per gram. The sensitivity is suboptimal. Please provide plans to improve assay sensitivity.
22. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
23. Revise your animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

APPENDIX 6: DS Microbiology Deficiency Items – May 3, 2010

Deficiencies in Drug Substance Microbiology (from DMF Deficiency Letter sent to (b) (4) dated May 3, 2010; Master File (b) (4)):

1. Provide a justification for all in-process holding times associated with the manufacture of Pancreatin using the 1206 and 1208 manufacturing processes. The processing times and holding conditions prior to the (b) (4) step” are of particular importance since most of the microbial proliferation occurs during that stage of the manufacturing process.
2. Provide the following information regarding in-process microbial alert and action levels for the 1206 and 1208 Pancreatin manufacturing processes:
 - a. The total aerobic microbial count (TAMC) alert and action levels for (b) (4) samples collected following (b) (4) but immediately before the addition of (b) (4) to the (b) (4). TAMC alert and action levels should be commensurate with those obtained from (b) (4) gland samples as reported in the 16 April 2010 submission to the agency.
 - b. TAMC alert and action levels for samples of the (b) (4) collected immediately prior to (b) (4)
 - c. A summary of the actions taken when alert and action levels are exceeded
3. Provide an explanation for the wide range of TAMC prior to the addition of (b) (4) for 1206 pancreatin lots (b) (4) CFU/g in 39 lots as compared to (b) (4)/g in 11 lots) in the data provided in attachment 5 of the 16 April 2010 submission. Provide a list of corrective actions to be taken to ensure that acceptable bioburden levels are achieved prior to the addition of (b) (4) to the (b) (4).
4. According to the manufacturing procedure listed on pages 790-791 of volume 24.14 of DMF (b) (4), the 1206 (b) (4) process can take place for (b) (4). Explain the rationale for determining which process to use and correlate the TAMC counts obtained in the 1206 process samples (attachment 5 of the 16-April-2010 document) with the holding times and temperatures used for each batch.
5. Step f) (1) of the 1208 process description states that (b) (4). Provide the maximum storage time for the 1208 (b) (4) prior to (b) (4).
6. Provide the following information regarding testing for the diarrheal form of *Bacillus cereus* enterotoxin:
 - a. A commitment to test each batch of Pancreatin drug substance for *Bacillus cereus* enterotoxin prior to release
 - b. A description of the *Bacillus cereus* enterotoxin test method, the validation procedure, and a summary of the supporting validation data.

APPENDIX 7: Summary of HHE Review – February 23, 2010

The following is summarized from a Health Hazard Evaluation (HHE) Review dated February 23, 2010:

A HHE Review was conducted by Anil Rajpal because of findings from an (b) (4) inspection related to microbial contamination. The request for the HHE consult (from the Office of Compliance, Division of Manufacturing and Product Quality) stated that during the recent FDA inspection and analysis of samples from (b) (4) *Bacillus cereus* was found in seven samples, and the *Bacillus cereus* enterotoxin was found in one sample. Preliminary microbiological results from the Pacific Regional Laboratory were provided; the highest levels measured were 240 Most Probable Number [MPN]/g in one sample, and 93 MPN/g in another sample; the remainder of the samples had levels of 43 MPN/g or less. (Levels of *Bacillus cereus* measured in MPN/g can be considered interchangeable with levels measured in Colony Forming Units [CFU]/g.)

The key conclusions of the HHE Review were as follows:

“...the levels found on inspection are considerably lower than the cutoff for causing illness (10^6 CFU/g) as per the draft guidance [*draft guidance for FDA staff entitled “Sec 527.300 Dairy Products-Microbial Contaminants and Alkaline Phosphatase Activity”*]. However, there still exists a small but potential risk with the levels that were measured. [*reference to e-mail from Dr. Benjamin Lorenz dated February 12, 2010*] In addition, presence of the enterotoxin if present even in minute quantities in the final drug product could produce or worsen symptoms of diarrhea. [*reference to e-mail from Dr. Benjamin Lorenz dated February 12, 2010*] There is a plan to evaluate drug product for detectable enterotoxin and to assess whether the amount of enterotoxin present can be measured in the drug substance and/or drug product.”

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/s/

ANIL K RAJPAL
01/27/2011

Medical Officer NDA Memo

Division of Gastroenterology Products

NDA #:	22-175
Applicant:	Digestive Care, Inc.
(Proposed) Trade Name:	Pertzye
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Dosing Regimen:	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Formulation:	For oral administration
Letter Date/Received Date:	July 29, 2010
PDUFA Goal Date	January 29, 2011
Date Review Completed:	January 14, 2011
Clinical Reviewer:	Marjorie F. Dannis, MD
Team Leader:	Anil Rajpal, MD

The Applicant submitted a 4-month safety update to NDA 22-175 on March 17, 2009, which was reviewed with the original submission.

According to the Applicant, “since that time to the current date, one (1) additional patient was enrolled in Protocol 092206 and completed the study with no adverse events (AEs) reported. There are no additional data from nonclinical or clinical studies/trials to report for a safety update.” On September 27, 2010, DCI submitted a statement reaffirming that there was no additional safety information to include with the current resubmission.

Thus, this reviewer’s conclusions regarding safety have not changed from the conclusions stated in the medical officer review of the original submission dated August 27, 2009.

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/s/

MARJORIE F DANNIS
01/14/2011

ANIL K RAJPAL
01/14/2011
I concur with Dr. Dannis.

Cross-Discipline Team Leader Review

Date	August 27, 2009
From	Anil Rajpal, MD, Acting Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-175
Applicant	Digestive Care, Inc.
Date of Submission	October 27, 2008
PDUFA Goal Date	August 27, 2009
Proprietary Name / Established (USAN) names	Pancrecarb® pancrelipase
Dosage forms / Strength	Pancrecarb® (pancrelipase) delayed release-capsules for oral administration, in USP units <ul style="list-style-type: none"> ▪ [REDACTED] (b) (4) ▪ Pancrecarb 8,000 lipase/[REDACTED] (b) (4) ▪ Pancrecarb 16,000 lipase/[REDACTED] (b) (4)
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Complete Response (CR) under 21 CFR 314

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1. Introduction

This submission, received October 27, 2008, is the initial New Drug Application (NDA) for Pancrecarb (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP). Pancrecarb 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.)

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.

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

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

- (1) Cotazym (NDA 20-580): approved in 1996; not currently marketed
- (2) Creon (NDA 20-725): approved April 30, 2009

Thus, there is only one approved PEP, Creon, that is 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: <ul style="list-style-type: none"> ▪ 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: A Risk Evaluation and Mitigation System (REMS) was implemented for Creon 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. (See also Section 2.1 and Appendix 1.)
- (2) Risk of Transmission of Viral Disease to Patients: There is a concern that because Creon 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 the Creon application; 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.

2.2.2 Regulatory History of Pancrecarb

Each of the three strengths of this product (MS-4, MS-8 and MS-16) have been marketed in the United States since 1995, 2000, and 2004 respectively, and are currently marketed under the name “Pancrecarb.” It is not known if the Currently Marketed Product (CMP) and the To be Marketed Product (TbMP) are the same formulation.

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

Table 2. Pertinent Regulatory History of Pancrecarb

Date	Action
May 1994	Original IND submission*
June 2005	Meeting with the Division to discuss NDA submission requirements
October 2005	Meeting with the Division to follow-up on CMC issues from June 2005 meeting
June 2006	Special Protocol Assessment for Pivotal Study (06-001) submitted
February 2007	Meeting with the Division to discuss CMC requirements for NDA submission
November 2007	Fast Track Designation granted
October 2008	NDA 22-175 submitted for Pancrecarb

* IND 45223

See the Clinical Review by Marjorie Dannis for details of the Pancrecarb regulatory history.

2.3 Current Submission

The NDA submission was received on October 27, 2008. It was classified as a ten-month submission with a PDUFA deadline of August 27, 2009.

No Advisory Committee meeting was convened to discuss this application.

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

- (1) Clinical Review by Marjorie Dannis, dated August 27, 2009
- (2) Statistics Review by Freda Cooner, dated July 21, 2009
- (3) CMC Reviews from Division of Therapeutic Proteins (DTP):
 - (a) CMC Review of Drug Product by Wei Guo (DTP), dated August 25, 2009

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.

- (b) CMC Review of Drug Substance Viral Issues (DMF (b)(4)) by Howard Anderson (DTP), dated August 27, 2009
- (c) CMC Review of Drug Substance Non-Viral Issues (DMF (b)(4)) by Wei Guo (DTP), dated August 27, 2009
- (4) Microbiology Review by Vinayak Pawar, dated May 13, 2009
- (5) ONDQA Reviews:
 - (a) ONDQA Review by Bogden Kurtyka, dated April 27, 2009
 - (b) ONDQA Review by Bogden Kurtyka, dated July 22, 2009
- (6) Pharmacology/Toxicology Review by Tamal Chakraborti, dated June 19, 2009
- (7) Clinical Pharmacology Reviews:
 - (a) Clinical Pharmacology Review by Peifan Bai, dated June 9, 2009
 - (b) Addendum to Clinical Pharmacology Review by Peifan Bai, dated August 26, 2009
- (8) DMEPA Reviews:
 - (a) DMEPA Tradename Review by Melina Griffis dated March 19, 2009
 - (b) DMEPA Label and Labeling Review by Melina Griffis dated May 8, 2009
- (9) DSI Review by Roy Blay, dated June 26, 2009

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 Viral Issues by Howard Anderson dated August 27, 2009, the CMC Review of Drug Substance Non-Viral Issues by Wei Guo dated August 27, 2009, the CMC Review of Drug Product by Wei Guo dated August 25, 2009, and the Microbiology Review by Vinayak Pawar dated May 13, 2009 for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (b)(4) the Drug Master File (DMF) holder (DMF (b)(4)); the DMF has been cross referenced by Digestive Care, Inc. (DCI) in NDA 22-175. DS is derived from porcine pancreas glands harvested from healthy pigs raised in (b)(4) as human food. The glands are obtained from slaughterhouses, which are under the inspection of the (b)(4). The glands are (b)(4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b)(4), which results in pancrelipase DS. The resulting pancrelipase DS is used for manufacture of drug product (DP).

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 review of drug substance viral issues. (b)(4) viral inactivation steps are involved in the DS manufacturing process, including (b)(4). To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses

program and provide an assessment of the ability of cleaning agents currently used in the facility to inactivate viral agents. If the cleaning agents are inadequate, provide a plan to implement appropriate cleaning agents to ensure inactivation of viral agents to prevent cross contamination between different batches of drug substance. Include a description of any additional procedures in place when dealing with equipment contaminations with a virus that possess a risk to product quality.

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1) for use in the lot release specifications for the drug substance.
3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release.
4. It is our understanding that the current sensitivity of viral detection assays does not appear to provide adequate assurance that released drug substance will be free of EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reovirus), Rota (Rota Virus), Influenza, VSV (Vesicular Stomatitis Virus), and PTV (Porcine Teschovirus) viruses. Provide the rationale why your proposed control strategy provides an appropriate level of control for these (for NDA 22-175) given the current estimate of the manufacturing process's ability to inactivate these viruses and the sensitivity of viral assays. This should include, calculation of estimated viral particles per dose (based on the limit of assay detection) for enveloped and non enveloped viruses per ICH guidance Q5A. If the estimated viral particles per dose is unacceptable you will need to improve the sensitivity of the qPCR assays used for monitoring viral load entering the manufacturing process and for drug substance release testing.
5. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
6. Revise your animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

DS Non-Viral Deficiency Items:

DS non-viral deficiency items to be communicated to (b) (4) (taken from Dr. Guo's review) are provided below. (See also Section 13.1.)

1. Please provide the results of the forced degradation studies used to evaluate the suitability of the RP-HPLC method.

2. Please define the amount of raw material used in the manufacturing of drug substance 1206.
3. Please provide a scientific justification as to why the acceptance criterion for (b) (4) is different between drug substance 1206 and 1208.
4. On page 47 of the 2008 annual update (Section 3.2.S.2) you refer to “finished product”. Please clarify what you define as “finished product”.
5. You have not submitted information on drug substance manufactured with the 1206 process. Please provide:
 - a. In-process control testing acceptance criteria for lipase activity and microbial limits (b) (4).
 - b. Acceptance range of yield for each critical manufacturing step and provide information supporting this range.
 - c. Operating and performance parameters for critical steps in the manufacture of 1206 and 1208.
 - d. Process validation data for 1206 drug substance.
 - e. (b) (4) enzyme activity characterization studies on drug substance 1206 using olive oil as substrate.
6. In your release testing program of drug substance 1206 and 1208, establish acceptance criteria with upper and lower limits for peak areas for all peaks identified by RP-HPLC.
7. In regards to your release and stability programs for drug substance 1206, we have the following comments:
 - a. Establish acceptance criteria for enzymatic activities with upper and lower limits.
 - b. Include additional, quantitative assays, but not limited to RP-HPLC, to measure product-related substances and impurities..
8. Provide trended stability data of drug substance 1206.
9. We recommend you expand your olive oil testing program to include monitoring for critical olive oil attributes. Please establish acceptance criteria for critical olive oil components (i.e. oleic acid), based on your historical testing results.
10. Please submit the following enzyme method validation study protocols and reports to the DMF: Lipase (b) (4) Protease (b) (4) and Amylase (b) (4)
11. Please identify an expiry or hold time for 1206 and 1208 drug substance before (b) (4) and provide data supporting your proposal.
12. Your testing program for the 1206 (b) (4) is not adequate. Specifically, we have the following comments:

- a. Please update the testing protocol to include additional tests for measurement of impurities, such as HPLC.
 - b. Please revise your acceptance criteria for enzyme activity by establishing upper and lower limits. Established acceptance criteria for all the tests performed.
 - c. Please provide a clear description of the LOD method and clarify the unit of measurement.
13. Due to the potential inconsistencies and reliance on USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
14. Please submit the results of the study conducted to demonstrate the equivalency of the (b) (4)

DP Issues

A number of CMC deficiencies were identified by the DP reviewer (see Review of Drug Product by Wei Guo dated August 25, 2009). An overview of deficiency items is provided below followed by the complete list of deficiency items to be communicated to the Applicant in the Complete Response (CR) letter.

Overview of DP Deficiency Items:

Deficiencies in broad categories relate to: (a) release testing, (b) stability testing, (c) process / process validation, (d) acceptance criteria / reference standards, (e) control of excipients, (f) CMP versus TBMP formulations, and (g) discrepancies between manufacturing dates and Certificate of Analysis signature dates. Each of these is summarized below along with the corresponding item number(s) of deficiencies (from the list of deficiencies to be sent in the CR letter).

- (a) Release Testing: An analytical test such as HPLC was not included to control for product- and process-related impurities; also, analytical tests to monitor particle size, target weight of pellets/capsule, and capsule disintegration time were not included. (See Item #1 in Deficiency Items to be Communicated to Applicant section below.) Drug product release test sampling plans were requested (see Item #12).
- (b) Stability Testing: The following deficiencies were identified: (a) analytical techniques such as HPLC that monitor product degradation were not included; (b) acceptance criterion for lipase activity should be revised to have an upper and lower limit; (c) explanation for (b) (4) trending in dissolution profile over a 12-month period in a subset of lots was not provided; (d) separate acceptance criteria for (b) (4) (b) (4) (e) real-time stability data to support a 24-month expiry; (f) rationale for (b) (4) in addition to gelatin capsules and justification for no additional stability or clinical data; (g) forced degradation studies (e.g., photostability, moisture conditions) were not provided to support stability of the product

once the final container is opened; and (h) testing for (b) (4) should be included. (See Item #2.)

- (c) Process / Process Validation: Sufficient information was not provided for evaluation of the (b) (4) steps in the manufacturing process (see Item #3), and for evaluation of whether (b) (4) the 1206 and 1208 drug substances (each manufactured by different processes) will result in a homogeneously (b) (4) DS (see Item #4). A complete process validation report was requested (see Item #14).
- (d) Acceptance Criteria / Reference Standards: Sufficient information was not provided to demonstrate that the (b) (4) activity is well controlled in this product (see Item #5), to evaluate the olive oil qualification program (see Item #6), and to evaluate the qualification program for incoming 1206 and 1208 drug substances (see Item #7). The Applicant is requested to use an internal reference standard that reflects the DP commercial manufacturing process in addition to the pancrelipase DS reference standard (see Item #8). The Applicant is requested to develop and implement a method to ensure accurate and consistent lipase activity for the working reference standard (see Item #9). The Applicant is requested to assess linearity for the lipase and protease assays using 5 data points rather than (b) (4) data points (see Item #10).
- (e) Control of Excipients: The Applicant is requested to provide detailed information regarding CMC for the cellulose acetate phthalate and diethyl phthalate used for (b) (4) of the product (see Item #11). The Applicant is requested to provide representative Certificates of Analysis (CoAs) and testing results of excipients used (see Item #15). The Applicant is requested to provide CMC information including (b) (4) content for (b) (4) Ink as the DMF referenced for (b) (4) Ink is closed (see Item #16).
- (f) CMP vs. TBMP Formulations: The Applicant is requested to provide a comparison of the Currently Marketed Product (CMP) and the To be Marketed Product (TbMP) formulations (see Item #13).
- (g) Discrepancies Between Manufacturing Dates and CoA Signature Dates: The Applicant is requested to explain discrepancies between the manufacturing dates of drug products lots, and the dates the CoAs were signed; in some cases, over two years elapsed between manufacturing and CoA sign off (see Item #17).

Deficiency Items to be Communicated to Applicant:

The full list of CMC deficiencies identified by the DP reviewer for communication to the Applicant in the CR letter is provided below (see Drug Product Review by Dr. Wei Guo):

1. Your release testing program is inadequate. Specifically, we have identified the following deficiencies:
 - a. You have not included an analytical test to control for product-related and process-related impurities. Product and process-related impurities should be monitored and appropriate acceptance criteria, based on process capability, manufacturing history and clinical experience should be

- developed and implemented. An analytical methodology such as, but not limited to, HPLC would be suitable to assess the purity of your product.
- b. You have not included analytical tests to monitor particle size, target weight of pellets/capsule and capsule disintegration time. Appropriate analytical methodologies should be used and acceptance criteria established.
2. Your stability program does not provide assurance that product stability is adequately controlled. Specifically, we have identified the following deficiencies:
 - a. You have not included analytical techniques that monitor product degradation such as, but not limited to, HPLC.
 - b. The acceptance criterion for lipase activity should be revised to include an upper and lower limit.
 - c. The stability data you have provided indicate that some drug product lots show a clear (b) (4) trending in the dissolution profile over a 12-month period whereas some other lots maintain a stable dissolution profile. Please provide an explanation for these inconsistencies in the stability data.
 - d. You are currently reporting (b) (4) content as a combination of all (b) (4) measured. Please provide acceptance criteria for each of the (b) (4) separately.
 - e. Expiry dating for a protein product is based on real-time and real-temperature stability data. You have not provided real-time stability data to support a 24 month expiry.
 - f. Please provide your rationale for using (b) (4), in addition to gelatin capsules, and justify why additional stability or clinical data are not necessary.
 - g. You have not provided a study that addresses the stability of the product once the final container is opened in the pharmacy or by the patient. Please provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.
 - h. Please update your stability protocol to include (b) (4) testing at all test stations.
 3. You have not provided sufficient information to the Agency to evaluate the (b) (4) steps in your manufacturing process. Please provide studies you have conducted and documentation of procedures you have in place to support (b) (4)
 4. You are (b) (4) drug substances manufactured by different processes (1206 and 1208) to achieve a defined target lipase activity. However, you have not provided sufficient information to evaluate whether the (b) (4) step in your manufacturing process will result in a homogeneously (b) (4) drug substance. Please provide validation studies that address the homogeneity of the (b) (4) drug substance used to manufacture (b) (4) MS8 and the homogeneity of the (b) (4) drug substance used to manufacture MS16.

5. Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) activity must be ensured in drug product. Please provide information that demonstrates you have control of (b) (4) activity in drug substance and product.
6. You have not submitted sufficient information in the NDA 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.
7. Please provide a description of your qualification program for incoming 1206 and 1208 drug substances.
8. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. 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.
9. Due to the potential inconsistencies and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
10. In regards to your analytical methodologies, we have the following comments:
 - a. The assessment of linearity for the lipase and protease assays is conducted using (b) (4) data points. We recommend a minimum of 5 data points for determination of assay linearity.
 - b. Please clarify your acceptance criteria for lipase assay linearity.
 - c. To support validation of (b) (4) assay precision, please clarify the amounts of (b) (4) and (b) (4) used during assay validation.
11. Please provide detailed information regarding the chemistry, manufacturing and controls for the cellulose acetate phthalate and diethyl phthalate used for (b) (4) of the product.
12. Please provide the drug product release test sampling plans.
13. Please provide a comparison of the formulation of the To be Marketed Product (TbMP) and the Currently Marketed Product.
14. We do not have sufficient information to evaluate your process validation. Please provide the following information:
 - a. The process validation report, with all relevant supporting data to demonstrate that your process is adequately controlled.

- b. Clarify the method used to assess the yield in (b) (4) of drug product manufacturing.
15. Please provide representative vendor COAs and your testing results of the excipients used in the manufacturing of (b) (4) MS-8 and MS-16.
16. The DMF you have referenced for the (b) (4) Ink, DMF (b) (4) is closed. Please provide CMC information, including (b) (4) content, for (b) (4) Ink.
17. We noticed discrepancies between the manufacturing dates of drug products lots, and the dates the Certificate of Analyses were signed. In some cases, over two years elapsed between manufacturing and CoA sign off. Please explain these discrepancies.

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.

Other Issues

DCI Inspection: The field investigator noted deficiencies in the facility inspection of DCI.

(b) (4) Inspection: The Drug Product reviewer notes that a facility inspection of (b) (4) was conducted in (b) (4) and a FDA Form 483 with (b) (4) observations was issued. Dr. Guo states that the GMP status of (b) (4) is under evaluation, and that determination of GMP status will be made after reviewing (b) (4) response to each of the findings. (See Drug Product Review by Dr. Wei Guo dated August 25, 2009.)

Consult with DAIOP: The Division of Anti-infective and Ophthalmology Products (DAIOP) was consulted because of findings from the (b) (4) inspection described above related to microbial contamination. The consult memo by Dr. Benjamin Lorenz is provided in Appendix 3. The consult was filed under NDA 22-222 (Ultrase) as (b) (4) is the DS manufacturer for that product as well as for Pancrecarb. The conclusions of Dr. Lorenz were as follows:

“The contamination by these (b) (4) organisms varied by lot and stage of processing. The consequence of ingesting this drug product orally with the levels of contamination found is difficult to predict. Since most of these organisms are likely (b) (4), it is not surprising the array of organisms that were found. These organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans, so it may not necessarily constitute a significant risk for most

immunocompetent individuals. Of the organisms found, the most concerning are the *Bacillus* spp., the effects of which might only predictably produce mild diarrhea. However, in patients with neutropenia, other major immunocompromise or anatomic derangements (as may be the case in patients with cancer or chronic pancreatitis), the risk could entail systemic illness. Since manufacturing levels exist for these particular organisms, and potentially immunocompromised patients may be exposed, the appropriate measures should be instituted to rectify this. Consider testing the final product for microbial and toxin contamination as well.”

Upon further discussion at a meeting that included Dr. Lorenz, it was determined that it would not be feasible to test the final product for microbial and toxin contamination.

3.2 Recommendation

A Complete Response Action is the overall recommendation by CMC.

The DP Review states the following: “The data submitted in this application do not support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. Issues that preclude approval of this application include inadequate release and stability testing, inadequate process validation and inadequate stability data to support an assignment of expiry.”

The DP and DS Reviews note that there are deficiencies identified in the NDA and in the DMF that preclude approval of this application. The DP issues should be communicated to the Applicant in the CR letter; the DS issues should be communicated to the DMF Holder in a separate letter. One deficiency item in the CR letter (Item #18) will state that a letter will be sent to the DMF Holder. (See Section 13.1 Recommended Regulatory Action.)

4. Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Tamal Chakraborti dated June 19, 2009, for complete information.

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance⁶, 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 Pancrecarb clinical development program. However, toxicology studies are needed if the excipients in the Pancrecarb 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, no new

⁶ 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/6275f1.htm>> April 2006.

pharmacology or toxicology studies were conducted with Pancrecarb and no new non-clinical studies were submitted in the NDA submission. The non-clinical information provided by the Applicant in the submission was from the published literature for the excipients in the clinical formulation of Pancrecarb.

Dr. Chakraborti notes that in a FDA communication dated July 11, 2006, the Division recommended that a comprehensive summary with sufficient details of chronic toxicology studies for the excipients would be needed for the NDA. DCI provided a comprehensive summary of the toxicology data available for each excipient used in the formulation of Pancrecarb. Dr. Chakraborti notes that based on the available toxicology data for each excipient used in the Pancrecarb 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. Chakraborti concludes that there appears to be no anticipated risks associated with the use of Pancrecarb at the proposed clinical doses in patients with EPI.

Dr. Chakraborti recommends an Approval action based on the non-clinical review of the information submitted in the NDA. Dr. Chakraborti 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: “Pregnancy Category C: Animal reproduction studies have not been conducted with Pancrecarb. It is not known whether Pancrecarb can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancrecarb capsules should be given to a pregnant woman only if clearly needed.”
- Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility): Wording in the Carcinogenesis, Mutagenesis and Impairment of Fertility section should be revised to:  (b) (4)

Since Pancrecarb is not recommended for Approval during this review cycle, the proposed labeling changes will be planned for negotiation with the Applicant should Pancrecarb receive an Approval action during a subsequent review cycle.

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 Peifan Bai dated June 9, 2009, and the Addendum to the Clinical Pharmacology Review by Peifan Bai dated August 26, 2009, for complete information.

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

In Vivo Intubation Study (Bioavailability Study):

This was an open-label, placebo-controlled, crossover study that evaluated the bioavailability of Pancrecarb in seven patients with EPI. Five capsules of Pancrecarb MS-16 or placebo were taken with the Lundh test meal (a liquid test meal containing protein, fat, and sugar); gastric and duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Based on the clinical pharmacology reviewer's calculation after taking into account the lipase activity recovered following placebo, there appears to be only a small amount of % lipase activity (<10%) recovered following Pancrecarb. The reviewer commented that clogging of catheters might have influenced the outcome of duodenal lipase recoveries. 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.

In Vitro Stability Study (Stability Study):

The percentages of lipase activities recovered after mixing with applesauce were determined for all three (b) (4) strengths. The results are listed below.

Mean (SD) % lipase activities after exposure to applesauce at room temperature are shown in the table below.

Table 3. Mean (SD) % Lipase Activities After Exposure to Applesauce at Room Temperature

	Dosage Strength Formulations		
	MS-4	MS-8	MS-16
Exposure Duration	40 minutes	60 minutes	50 minutes
Lipase activity	90% (3.5%)	91% (3.8%)	93% (3.6%)

(Table above modified from table in Dr. Bai's Clinical Pharmacology Review dated June 9, 2009.)

Upon initial review (see Dr. Bai's Clinical Pharmacology Review dated June 9, 2009), Dr. Bai concluded the following: (a) Based on the above results for individual strengths, the lipase activities recovered after mixing with applesauce were higher than the current standard of at least 90%. (b) Pancrecarb microspheres, MS-4, MS-8 and MS-16, were stable after exposure to applesauce at room temperature for 40 min, 60 min, and 50 min, respectively. (c) The study results support the use of applesauce as a medium to facilitate ingestion of Pancrecarb microspheres.

Dr. Bai revised the assessment of the *in vitro* stability study (see Dr. Bai’s Addendum to Clinical Pharmacology Review dated August 26, 2009) after the CMC reviewer had identified a product deficiency (see Item #10 of Deficiency Items) related to measurement of lipase activity. Dr. Bai’s final recommendation is for the Applicant to repeat the *in vitro* stability study using the analytical method described in Deficiency Item #10 (i.e., use of a minimum of 5 data points for determination of assay linearity rather than ^(b)₍₄₎ data points) but otherwise the same study design as that submitted.

5.2 Recommendation

A Complete Response Action is the recommendation by the Clinical Pharmacology discipline (see Deficiency Item # 19 in Section 13.1 Recommended Regulatory Action).

6. Clinical Microbiology

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

7. Clinical/Statistical - Efficacy

7.1 Issues

The reader is referred to the Clinical Review by Marjorie Dannis dated August 27, 2009, and the Statistical Review by Freda Cooner dated July 21, 2009, for complete information.

Each of the three strengths of this product (MS-4, MS-8 and MS-16) have been marketed in the United States since 1995, 2000, and 2004 respectively, and are currently marketed under the name “Pancrecarb.” It is not known if the Currently Marketed Product (CMP) and the To be Marketed Product (TbMP) are the same formulation.

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

Clinical Studies

The pivotal study (06-001) and the supportive study (97-001-1B) were reviewed in depth by the Clinical Reviewer. Pertinent features of these studies are summarized in the table below.

Table 4. Selected Pancrecarb Clinical Studies

Study No.	Design	Product	Primary Endpoint / Objective	No. of Pts	Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo-controlled, two-way crossover	MS-16 and Placebo	Change in CFA	21	8-43	CF

97-001-1B	Randomized, open-label, active-control two-way crossover	MS-8	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19	12-27	CF
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(Table above is modified from table found in Clinical Review by Marjorie Dannis.)

A full listing of Pancrecarb clinical studies is provided in Appendix 2.

Efficacy Results

Study 06-001

The primary efficacy endpoint in the pivotal study 06-001 was the comparison of percent coefficient of fat absorption (% CFA) to a % CFA on placebo treatment. % CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet. The formula for the % Coefficient of Fat Absorption (CFA) is provided below:

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

In severely affected patients (i.e., patients with a baseline % CFA of $\leq 40\%$), a clinically meaningful change in % CFA is considered to be an increase of $\geq 30\%$. For patients with baseline % CFA $> 40\%$, no accepted change in % CFA has been established. More severely affected patients (i.e., patients with lower baseline % CFAs) are expected to experience larger increases in % CFA with PEP treatment than less severely affected patients (i.e., patients with higher baseline % CFAs).

The pivotal study, 06-001, was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pancrecarb MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI). Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pancrecarb MS-16 and placebo. Pertinent features of the study design are summarized in the table below.

Table 5. Pertinent Features of Study Design

Study Days	Period*	Treatment
-14 to -10	Screening Period (4 days)	--
-10 to 0	Dose Stabilization Period (7-10 days)	Pancrecarb
1 to 2 (home) 3 to 6 (GCRC)	Treatment Period 1 (6-8 days)	Pancrecarb or Placebo
7 to 10	Washout/Re-stabilization Period (7-10 days)	Pancrecarb
1 to 2 (home) 3 to 6 (GCRC)	Treatment Period 2 (6-8 days)	Pancrecarb or Placebo

* The follow-up period includes the end of the study visit (14 days after discharge at the end of Treatment Period 2)
GCRC: General Clinical Research Center

(The table above is modified from a figure and supporting text found in the Clinical Review by Marjorie Dannis.)

Doses in this study were not to exceed a maximum lipase dose of 2500 lipase units/kg/meal, which is in agreement with CFF recommendations (see Appendix 1). The dose for each subject (for the Dose Stabilization Period and Treatment Periods) was selected as follows:

- **Dose Stabilization Period:** During the Dose Stabilization Period, a high-fat diet (approximately 2 gm fat/kg/day) was consumed. The patient's Pancrecarb MS-16 dose

was managed in order to achieve control of pancreatic insufficiency symptoms and to achieve stabilized status according to the clinician’s observations and subject’s signs and symptoms.

- **Treatment Periods:** The dose chosen during the Dose Stabilization Period was used during the subsequent Treatment Periods.

The results of the study show that 29 patients were enrolled in the study, and 24 patients were randomized. Twenty-one patients completed the study. Three patients discontinued the study after randomization (two for adverse events, and one for a protocol violation).

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

Table 6. Demographics of Study 06-001

	Children < 18 (n=11)	Adults ≥ 18 (n=13)	Overall (n=24)
Age (years)			
Mean (SD)	12 (2.9)	27(7.4)	20(9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

(Table above is taken from the Clinical Review by Marjorie Dannis.)

The mean age overall was 20 years (range 8 to 43 years). In children (≥ 7 to 17 years), the mean age was 12 years. In adults (≥ 18 years), the mean age was 27 years. More males than females were enrolled in both age groups (overall: 18 males, 6 females; children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly Caucasian (92%) which is consistent with the racial/ethnic prevalence of this disease.

The mean CFA for patients receiving Pancrecarb was 83%; the mean CFA for patients receiving placebo (no treatment) was 46%. The mean change in CFA was 36% (p <0.001; 95% CI [28, 45]). The FDA Statistician confirmed the results and was agreement with the Applicant. The results are summarized in the table below.

Table 7. Comparison of %CFA (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162 ^a	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007 ^a	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317 ^a	25.848, 48.786

^a P<0.001

(Table above is taken from the Clinical Review by Marjorie Dannis; source was listed as 06-001 Study Report.)

A simple t-test for two independent samples or a paired t-test was performed by the Statistical Reviewer; similar results were seen. (See Statistical Review by Freda Cooner.)

The clinical reviewer and statistical reviewer also performed analyses of the primary endpoint in subgroups defined by placebo CFA (<40% and \geq 40%). The results (from the Statistical Review) are shown below:

Table 8. Comparison of CFA Stratified by Placebo CFA (% , Completed-Treatment Population) for Study 06-001

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Placebo CFA < 40%				
Overall (n = 9)	76.990	25.298	51.692 ^a	(38.390, 64.994)
Children (n = 5)	73.629	24.871	48.758 ^a	(29.947, 67.570)
Adults (n = 4)	80.350	25.725	54.625 ^a	(35.813, 73.437)
Placebo CFA \geq 40%				
Overall (n = 12)	86.676	61.018	25.658 ^a	(18.008, 33.307)
Children (n = 5)	86.607	62.752	23.855 ^b	(12.075, 35.635)
Adults (n = 7)	86.745	59.284	27.461 ^a	(17.529, 37.293)

^a P < 0.001

^b P = 0.0013

Source: Reviewer's Table

(Table above is taken from the Statistics Review by Freda Cooner.)

The patients who had a placebo CFA \geq 40% showed smaller increases in CFA after treatment with Pancrecarb than patients who had a placebo CFA < 40%. The statistical reviewer noted that using the t-tests, these results did not change.

The statistical reviewer commented that although it can be concluded that there is an overall treatment effect of Pancrecarb MS-16 on CFA, it is not known whether Pancrecarb MS-16 would improve CFA for the patients with placebo CFA levels greater than 80% due to lack of data in that subgroup.

Study 97-001-1B

The supportive study, 97-001-1B, was a multicenter, randomized, open-label, active-controlled, two-way crossover study evaluating the efficacy and safety of Pancrecarb MS-8. This study, in 19 patients with a confirmed diagnosis of CF and EPI, was designed to compare measures of fat malabsorption before (while on usual PEP treatment) and after oral administration of Pancrecarb MS-8 at an approximately 50% reduced lipase dose.

Dosage: The dosage of Pancrecarb MS-8, the test pancreatic enzyme, and the reference pancreatic enzymes [Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18, and MT-20 (Axcen/Scandipharm)] were adjusted to approximately 50% of each patient's routine lipase dose requirement, but not lower than approximately 1,800 USP units of lipase per gram of fat intake per day.

Overview of Study Design:

- Screening Visit: At the time of the screening visit, all patients had received pancreatic enzyme therapy in the form of Creon®, Pancrease®, or Ultrase®. After determination of

the current lipase dose, the existing enzyme therapy dose was reduced by approximately 50%, but no lower than approximately 1800 units of lipase per gram of fat intake per day. Only those patients with a CFA < 85% during the initial approximately 50% reduced enzyme dose were randomly assigned in the two crossover treatment periods.

- **Treatment Periods:** The study was carried out during two consecutive seven-day treatment periods in patients with CF. These reduced lipase doses were maintained throughout the study during each seven day treatment arm of the study. Following the first stool collection, the patients were instructed to collect stools for an additional three days on their reduced lipase dose.

The results of the study show [REDACTED] (b) (4)

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

Table 9. Summary of Baseline Demographics (ITT Population)

	Cincinnati site (n = 8)	Indianapolis site (n = 11)	Overall ^a (n = 19)
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6

^a The results are in agreement with those from the Applicant.

(Table above is taken from the Clinical Review by Marjorie Dannis.)

The mean age overall was 18 years (range 12 to 28 years). Approximately equal proportions of males and females were enrolled. The patients were mostly Caucasian (95%) which is consistent with the racial/ethnic prevalence of this disease.

The ITT results (see table below) [REDACTED] (b) (4)

[REDACTED] As per the Sponsor’s analysis, this change in CFA was statistically significant (see table below).

Table 10. Efficacy Results Study 97-001-1B

	Pancrecarb MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19)	[REDACTED]		(b) (4)
CFA (%)			
PP Population (n=18)	[REDACTED]		
CFA (%)			

* One patient (011) at the Indianapolis site was non-compliant to the protocol specified diet and was identified by the sponsor as a major protocol violation.

Table above is taken from the Clinical Review by Marjorie Dannis; source was listed as Statistical Reviewer’s Table.

The statistical reviewer commented: “Due to the fact that this study was open-label, had no washout period between two crossover treatment periods, used repeated treatment assessments, and had changes in the analysis plan, the results cannot reliably support an efficacy claim.”

Dosage Strength Formulations

Comparability of the (b) (4) formulations ((b) (4) MS-8, and MS-16) relative to one another was not shown by the information provided in the NDA submission. (b) (4)

[REDACTED]

The clinical and statistical reviewers each noted that although the pivotal study (06-001) demonstrated a treatment effect with the MS-16 formulation, the other controlled study (97-001-1B) lacked statistical rigor to support any efficacy claims of the MS-8 formulation, and there were no other controlled clinical studies submitted in support of demonstration of efficacy of MS-8 (b) (4). Thus, the reviewers were unable to determine the efficacy of the (b) (4) MS-8 formulations.

7.2 Recommendation

The Clinical Reviewer recommended that if an approval action was taken, only the MS-16 dosage strength formulation should be allowed for approval as the clinical data submitted in the NDA are adequate to label the MS-16 formulation for patients with EPI; the Statistical Reviewer agreed with this recommendation.

For the other dosage strength formulations ((b) (4) MS-8), the Clinical Reviewer recommends the following:



The above will be communicated to the Applicant in the CR letter (see Item #20 in Section 13.1 Recommended Regulatory Action).

8. Safety

The reader is referred to the Clinical Review by Marjorie Dannis dated August 27, 2009 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.^{7,8,9} (See also Appendix 1.) Continued monitoring for fibrosing

⁷ 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.

⁸ 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.

⁹ 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.

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.
- 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.^{10,11} (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 Marjorie Dannis dated August 27, 2009 for complete information.

Exposure

The safety population includes 262 subjects exposed to Pancrecarb covering a treatment period ranging from seven days to more than two years. (The safety population was defined as any subject who received at least one dose of Pancrecarb.)

¹⁰ Antiviral Drugs Advisory Committee (December 2, 2008);
<<http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs>>

¹¹ Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

The safety of Pancrearb was evaluated in ten clinical studies; Studies 06-001 and 97-001B have been described in detail in Section 7 of this review; the other eight studies are described in Appendix 2.

The overall exposure is summarized by study in the table below.

Table 11. Mean Lipase Doses and Duration of Dosing in Clinical Studies

Study No.	Duration of PANCRECARB® Treatment	Lipase Dose Measure	PANCRECARB® Mean Lipase Units		Comparator Mean Lipase Units	
06-001	7 days	Units/kg/meal	PANCRECARB® MS-16		Placebo	
			1,565 (SD 563)		n/a	
97-001-1B	7 days	Units/kg/meal	PANCRECARB® MS-8		Usual Enzyme*	
			1,158 (SD 429)		1,145 (SD 448)	
			Units/kg/day		4,237 (SD 1,873) ^a	4,189 (SD 1,913)
091897	Up to 2 years	Units/kg/day	PANCRECARB® MS-8		Initial History	
			4,576 (SD 3,071)		9,898 (SD 12,004)	
97-001-2	7 days	Units/kg/day	PANCRECARB® MS-8		Creon® 10 or 20	
			8,682 (SD 3,369)		16,519 (SD 7,207)	
071503	14 days	Units/kg/day	PANCRECARB® MS-16		Usual Enzyme*	
			5,430 (SE 510)		7,838 (SE 637)	
2001-180	30 days	Units/kg/day	PANCRECARB® MS-4		Viokase® powder ^b	
			4,490 (SE 1,251)		9,128 (SE 1,251)	
020296	14 days	Units/kg/day	PANCRECARB® MS-8 ^c		Cotazym® ECS-8	
			6,071 (SD 1,072)		6,810 (SD 1,860)	
111395	14 days (per phase)	Units/day	PANCRECARB® MS-8 ^c		Usual Enzyme**	
			Phase 2	Phase 3	Phase 1	
			273,143 (SD 153,014)		192,503 (SD 87,907)	323,200 (SD 153,823)
		Units/kg/day ^d	5,811		4,096	6,875
092100	7 days	Capsules/Day	PANCRECARB® MS-8		Placebo	
			6.9 (SD 2.8)		n/a	

*Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcen/Scandipharm)

**Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-16 (Ortho/McNeil); Ultrase® MT-20 (Axcen/Scandipharm); Cotazym® ECS-8 (Organon)

^a Units/kg/day represent an approximate 48% reduction from the patients' usual lipase dose of 8,760 units, calculated from the average of the range of the number of capsules per day at study entry.

^b Viokase® is a registered trademark of Axcen/Scandipharm.

^c A previous formulation (b)(4) PANCRECARB® (pancrelipase) MS-8 drug product was used in these studies.

^d Units/kg/day estimated using a mean body weight of 47kg.

n/a = not applicable

(Table above is taken from the Clinical Review by Marjorie Dannis; source is listed as the Applicant's submission.)

Postmarketing Experience (CMP): The manufacturer does not have specific data on the number of patients treated with Pancrearb. However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b)(4) Pancrearb

capsules were shipped to wholesalers. If the usual range of daily intake of Pancrecarb is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pancrecarb on an annual basis. It should be noted that it is not known if the CMP and the TBMP are the same formulations (see Section 3.1).

Safety Findings

Deaths: Four deaths were recorded during the 2-year long term (091897) study period; none were attributed to the use of Pancrecarb MS-8 (see Clinical Review). No other deaths were reported during any other study with Pancrecarb.

SAEs: Three Pancrecarb treated patients experienced four AEs (CF exacerbation and sinusitis in first patient, MVA in second patient, CF in third patient); each of these was considered serious by the study investigator(s). None of the SAEs were considered related to treatment (see Clinical Review). There were two additional hospitalizations (for exacerbation of CF) that were SAEs but not initially reported as such; these events were not considered to be related to enzyme treatment.

Dropouts and/or Discontinuations: Overall, 22 patients (8%) from the total safety population of 262 discontinued for reasons attributed to AE(s); 18 of those 22 were receiving Pancrecarb. The long-term study (091897) contributed 13 of the 18 Pancrecarb patients who discontinued due to AE(s). The majority of the AEs were gastrointestinal in nature. The Applicant reported that an additional seven patients discontinued Study 091897 for reasons noted to be due to AE(s) on the CRF clinical summary page, but due to insufficient information, these events were not included in the ISS AE database. The clinical reviewer examined the reports for each of these seven patients, and noted that each of the discontinuations was gastrointestinal in nature (see Clinical Review).

Hypersensitivity Reactions: Two cases of hypersensitivity reactions were reported:

- In Study 06-001, a 17-year-old female experienced a mild rash during treatment phase 2 (Pancrecarb MS-16) which was considered unrelated to study medication, and which resolved with concomitant medication.
- In Study 97-001B, a 17-year-old male experienced a moderate intensity rash during treatment phase 2 (Pancrecarb MS-8) which was considered possibly related to study medication. No action was taken and the event resolved completely.

Common AEs: Of the 262 patients treated with Pancrecarb that were enrolled in a total of 9 clinical studies, 77 (29%) experienced 148 AEs. Of these, 36 (14%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. The most commonly reported AE (>5% incidence) in the Pancrecarb treated safety group was abdominal pain, with 14 events reported, 11 of which were considered related to treatment. There were 7 reports of severe abdominal pain, 6 of which were considered related to treatment. Other AEs reported for patients treated with Pancrecarb included upper abdominal pain and headache (n=8 each), diarrhea and flatulence (n=7 each), abdominal distension and frequent bowel movements (n=6 each).

Postmarketing Experience (CMP): Pancrecarb capsules were introduced onto the US market by Digestive Care, Inc. in 1995 as a physician prescribed pancreatic enzyme replacement therapy. Annual Drug Product Reviews have been prepared since 2002. Over this period of time, only two product complaints relating to an adverse drug reaction have been reported. A case of Distal Intestinal Obstructive Syndrome (DIOS) was reported that was determined to be congenital and not considered by the physician to be related to treatment with Pancrecarb, and one case of allergic reaction (itching and red, blotchy rash on face) in a patient with a history of allergy to another pancrelipase product. It should be noted that it is not known if the CMP and the TBMP are the same formulations (see Section 3.1).

Conclusion: The Clinical Reviewer concluded that the AE profile of Pancrecarb as described in the individual studies and in the pooled analysis 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 approval should Pancrecarb receive an Approval action during a subsequent review cycle. 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 Deficiency Item #21 in Section 13.1 Recommended Regulatory Action, and 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 not presented to the Pediatric Research Committee (PeRC) during this review cycle because Pancrecarb is not recommended for Approval during this review cycle. Presentation to PeRC may occur should Pancrecarb receive an Approval action during a subsequent review cycle.

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. Pancrecarb is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

The reader is referred to the DSI Review by Roy Blay, dated June 26, 2009 for complete information.

DSI inspections of two clinical sites of Study 06-001 were performed; these were Site 007 (Dr. Strausbaugh; Cleveland, Ohio; n=6) and Site 191 (Dr. Ahrens; Iowa City, Iowa; n=5). These sites were selected by the Division because each of these sites had large percentages of the overall study population; in addition, Site 007 had the highest mean change in the coefficient of fat absorption (%CFA) among study sites. The DSI Inspector commented that for each of the sites review of the records revealed no significant discrepancies/regulatory violations.

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

11.3 Drug Shortage

Currently, Creon is the only PEP that is available on the market that has 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. The impact of a Complete Response action for Pancrecarb on the possible development of a drug shortage in the near future (i.e., by April 28, 2010; the time that all marketed PEPs must have an approved NDA) is not known at the present time.

11.4 Facilities Inspection

During a recent inspection of Scientific Protein Laboratories and Digestive Care, Inc., the manufacturing facilities for this application, the field investigator conveyed deficiencies to the representative of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

12. Labeling

12.1 Proprietary name

A review of the trade name “Pancrecarb” was performed by Melina Griffis in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Tradename Review dated March 19, 2009). DMEPA objects to the use of the proprietary name, Pancrecarb, for this product. The results of the Proprietary Name Risk Assessment found the proposed name, Pancrecarb, (b) (4)



A label and labeling review was also performed by Melina Griffis in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated May 8, 2009). Using Failure Mode and Effects Analysis and lessons learned from post-marketing experience with the pancrelipase products, DMEPA evaluated the container labels, carton labeling and insert labeling. DMEPA’s findings indicate that the presentation of information in the labels and labeling (b) (4). Detailed reasons and recommendations are provided in the DMEPA Label and Labeling Review. Since Pancrecarb is not recommended for Approval during this review cycle, labeling changes will be planned for negotiation with the Applicant should Pancrecarb receive an Approval action during a subsequent review cycle.

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 misleading from a promotional perspective. This is documented in the Tradename review by Melina Griffis dated March 19, 2009.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

Since Pancrecarb is not recommended for Approval during this review cycle, labeling changes (to Physician Labeling, Medication Guide, and Carton and Container Labeling) will be planned for negotiation with the Applicant should Pancrecarb receive an Approval action during a subsequent review cycle.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The CMC Drug Product Reviewer recommends this NDA for CR because he identified a number of deficiency items in the application; these included deficiencies in release testing, stability testing, process validation, acceptance criteria, and reference standards. In addition, viral and non-viral Drug Substance deficiencies (identified by the CMC Drug Substance Viral Issues Reviewer and the CMC Drug Substance Non-Viral Issues Reviewer) will be communicated in a separate letter to the DMF Holder, (b) (4) (DMF (b) (4)).

The Clinical Pharmacology Reviewer recommended this NDA for CR; she requested that the *in vitro* stability study be repeated because the analytical method used to measure lipase activity was not adequately validated.

The Nonclinical Pharmacology/Toxicology Reviewer recommended this NDA for approval.

The Clinical Reviewer recommended that if an approval action was taken, only the MS-16 dosage strength formulation should be allowed for approval as the clinical data submitted in the NDA are adequate to label the MS-16 formulation for patients with EPI; the Statistical Reviewer agreed with this recommendation. The Clinical Reviewer identified a deficiency item for the other dosage strength formulations ((b) (4) MS-8). In addition, the Clinical Reviewer recommended that the Risk Evaluation and Mitigation Strategy (REMS) be required as part of approval should Pancrecarb receive an Approval action during a subsequent review cycle.

The following deficiencies identified by the CMC Reviewers, the Clinical Pharmacology Reviewer, and the Clinical and Statistical Reviewers should be communicated to the Applicant in the CR letter:

CR Letter to DCI (NDA 22-175):

CMC Deficiencies:

1. Your release testing program is inadequate. Specifically, we have identified the following deficiencies:
 - a. You have not included an analytical test to control for product-related and process-related impurities. Product and process-related impurities should be monitored and appropriate acceptance criteria, based on process capability, manufacturing history and clinical experience should be developed and implemented. An analytical methodology such as, but not limited to, HPLC would be suitable to assess the purity of your product.

- b. You have not included analytical tests to monitor particle size, target weight of pellets/capsule and capsule disintegration time. Appropriate analytical methodologies should be used and acceptance criteria established.
 2. Your stability program does not provide assurance that product stability is adequately controlled. Specifically, we have identified the following deficiencies:
 - a. You have not included analytical techniques that monitor product degradation such as, but not limited to, HPLC.
 - b. The acceptance criterion for lipase activity should be revised to include an upper and lower limit.
 - c. The stability data you have provided indicate that some drug product lots show a clear ^{(b) (4)} trending in the dissolution profile over a 12-month period whereas some other lots maintain a stable dissolution profile. Please provide an explanation for these inconsistencies in the stability data.
 - d. You are currently reporting ^{(b) (4)} content as a combination of all ^{(b) (4)} measured. Please provide acceptance criteria for each of the ^{(b) (4)} separately.
 - e. Expiry dating for a protein product is based on real-time and real-temperature stability data. You have not provided real-time stability data to support a 24 month expiry.
 - f. Please provide your rationale for using ^{(b) (4)}, in addition to gelatin capsules, and justify why additional stability or clinical data are not necessary.
 - g. You have not provided a study that addresses the stability of the product once the final container is opened in the pharmacy or by the patient. Please provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.
 - h. Please update your stability protocol to include ^{(b) (4)} testing at all test stations.
 3. You have not provided sufficient information to the Agency to evaluate the ^{(b) (4)} steps in your manufacturing process. Please provide studies you have conducted and documentation of procedures you have in place to support ^{(b) (4)}
 4. You are ^{(b) (4)} drug substances manufactured by different processes (1206 and 1208) to achieve a defined target lipase activity. However, you have not provided sufficient information to evaluate whether the ^{(b) (4)} step in your manufacturing process will result in a homogeneously ^{(b) (4)} drug substance. Please provide validation studies that address the homogeneity of the ^{(b) (4)} drug substance used to manufacture ^{(b) (4)} MS8 and the homogeneity of the ^{(b) (4)} drug substance used to manufacture MS16.
 5. Due to the critical role of ^{(b) (4)} in lipase activity, adequate control of ^{(b) (4)} activity must be ensured in drug product. Please provide information that demonstrates you have control of ^{(b) (4)} activity in drug substance and product.

6. You have not submitted sufficient information in the NDA 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.
7. Please provide a description of your qualification program for incoming 1206 and 1208 drug substances.
8. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. 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.
9. Due to the potential inconsistencies and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
10. In regards to your analytical methodologies, we have the following comments:
 - a. The assessment of linearity for the lipase and protease assays is conducted using ^(b) data points. We recommend a minimum of 5 data points for determination of assay linearity.
 - b. Please clarify your acceptance criteria for lipase assay linearity.
 - c. To support validation of ^{(b) (4)} assay precision, please clarify the amounts of ^{(b) (4)} and ^{(b) (4)} used during assay validation.
11. Please provide detailed information regarding the chemistry, manufacturing and controls for the cellulose acetate phthalate and diethyl phthalate used for ^{(b) (4)} of the product.
12. Please provide the drug product release test sampling plans.
13. Please provide a comparison of the formulation of the To be Marketed Product (TbMP) and the Currently Marketed Product.
14. We do not have sufficient information to evaluate your process validation. Please provide the following information:
 - a. The process validation report, with all relevant supporting data to demonstrate that your process is adequately controlled.
 - b. Clarify the method used to assess the yield in ^{(b) (4)} of drug product manufacturing.
15. Please provide representative vendor COAs and your testing results of the excipients used in the manufacturing of ^{(b) (4)} MS-8 and MS-16.

16. The DMF you have referenced for the (b) (4) Ink, DMF (b) (4), is closed. Please provide CMC information, including (b) (4) content, for (b) (4) Ink.
17. We noticed discrepancies between the manufacturing dates of drug products lots, and the dates the Certificate of Analyses were signed. In some cases, over two years elapsed between manufacturing and CoA sign off. Please explain these discrepancies.
18. The (b) (4) DMF # (b) (4) has been reviewed in support of NDA 022175 and found to contain deficiencies. A letter will be sent to (b) (4) listing the deficiencies. (b) (4) should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify us when (b) (4) has submitted the requested information.

Clinical Pharmacology Deficiency:

19. The submitted applesauce study (Protocol #080705) is not acceptable because the lipase assay method was not adequately validated (see PRODUCT QUALITY Comment #10 above). We recommend that you repeat the applesauce study with newly validated analytical methods and submit the results for our review. The use of applesauce as a mixing medium to facilitate product administration will be labeled based on the results of the repeat study, if found acceptable.

Clinical Deficiencies:

20. We were unable to determine the efficacy of the (b) (4) MS-8 formulations because the studies submitted (b) (4) were not adequate to demonstrate the effectiveness of the (b) (4) MS-8 formulations. In addition, comparability of the (b) (4) formulations (b) (4) MS-8, MS-16) relative to one another was not shown by the information provided in the NDA submission.



21. As described in our letter dated March 19, 2009, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Pancrearb (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) 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.

We acknowledge the submission of your REMS documents on July 31, 2009. Once FDA finds the content of your REMS acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

“Dispense the enclosed Medication Guide to each patient.” or

“Dispense the accompanying Medication Guide to each patient.”

Prominently identify submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022175
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

Letter to (b) (4) (DMF (b) (4)):

The following drug substance deficiencies should be communicated in a letter to the DMF Holder, (b) (4) (DMF (b) (4)):

Viral DS Deficiencies:

1. You have not provided a detailed description of the sanitizing/cleaning procedures in place to help prevent viral cross contamination between different batches of drug substance. Please provide a detailed description of your sanitization program and provide an assessment of the ability of cleaning agents currently used in the facility to inactivate viral agents. If the cleaning agents are inadequate, provide a plan to implement appropriate cleaning agents to ensure inactivation of viral agents to prevent cross contamination between different batches of drug substance. Include a description of any additional procedures in place when dealing with equipment contaminations with a virus that possess a risk to product quality.

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1) for use in the lot release specifications for the drug substance.
3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release.
4. It is our understanding that the current sensitivity of viral detection assays does not appear to provide adequate assurance that released drug substance will be free of EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reovirus), Rota (Rota Virus), Influenza, VSV (Vesicular Stomatitis Virus), and PTV (Porcine Teschovirus) viruses. Provide the rationale why your proposed control strategy provides an appropriate level of control for these (for NDA 22-175) given the current estimate of the manufacturing process's ability to inactivate these viruses and the sensitivity of viral assays. This should include, calculation of estimated viral particles per dose (based on the limit of assay detection) for enveloped and non enveloped viruses per ICH guidance Q5A. If the estimated viral particles per dose is unacceptable you will need to improve the sensitivity of the qPCR assays used for monitoring viral load entering the manufacturing process and for drug substance release testing.
5. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
6. Revise your animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

Non-Viral DS Deficiencies:

7. Please provide the results of the forced degradation studies used to evaluate the suitability of the RP-HPLC method.
8. Please define the amount of raw material used in the manufacturing of drug substance 1206.
9. Please provide a scientific justification as to why the acceptance criterion for (b) (4) is different between drug substance 1206 and 1208.
10. On page 47 of the 2008 annual update (Section 3.2.S.2) you refer to "finished product". Please clarify what you define as "finished product".
11. You have not submitted information on drug substance manufactured with the 1206 process. Please provide:

- a. In-process control testing acceptance criteria for lipase activity and microbial limits (b) (4).
 - b. Acceptance range of yield for each critical manufacturing step and provide information supporting this range.
 - c. Operating and performance parameters for critical steps in the manufacture of 1206 and 1208.
 - d. Process validation data for 1206 drug substance.
 - e. (b) (4) enzyme activity characterization studies on drug substance 1206 using olive oil as substrate.
12. In your release testing program of drug substance 1206 and 1208, establish acceptance criteria with upper and lower limits for peak areas for all peaks identified by RP-HPLC.
13. In regards to your release and stability programs for drug substance 1206, we have the following comments:
- a. Establish acceptance criteria for enzymatic activities with upper and lower limits.
 - b. Include additional, quantitative assays, but not limited to RP-HPLC, to measure product-related substances and impurities..
14. Provide trended stability data of drug substance 1206.
15. We recommend you expand your olive oil testing program to include monitoring for critical olive oil attributes. Please establish acceptance criteria for critical olive oil components (i.e. oleic acid), based on your historical testing results.
16. Please submit the following enzyme method validation study protocols and reports to the DMF: Lipase (b) (4) Protease (b) (4), and Amylase (b) (4).
17. Please identify an expiry or hold time for 1206 and 1208 drug substance before (b) (4) and provide data supporting your proposal.
18. Your testing program for the 1206 (b) (4) is not adequate. Specifically, we have the following comments:
- a. Please update the testing protocol to include additional tests for measurement of impurities, such as HPLC.
 - b. Please revise your acceptance criteria for enzyme activity by establishing upper and lower limits. Established acceptance criteria for all the tests performed.
 - c. Please provide a clear description of the LOD method and clarify the unit of measurement.
19. Due to the potential inconsistencies and reliance on USP lipase reference standard, we recommend the development and implementation of a method that

includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.

20. Please submit the results of the study conducted to demonstrate the equivalency of the (b) (4).

13.2 Risk Benefit Assessment

The benefit characteristics appear similar to those of already marketed PEPs for treatment of EPI. The outstanding risk issues with this application are the significant deficiencies identified from the CMC discipline (including release testing, stability testing, process validation, acceptance criteria, and reference standards from a drug product perspective, and both viral and non-viral issues from a drug substance perspective).

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

See Deficiency Item #21 (in CR Letter to DCI) in Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since Pancrecarb is not recommended for Approval during this review cycle, recommendations for postmarketing required pediatric studies will be made should Pancrecarb receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

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

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

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct:

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

The specific details of these required postmarketing studies will be described more fully in the approval letter for this application, if it is approved.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

Since Pancrecarb is not recommended for Approval during this review cycle, postmarketing commitments will be planned for negotiation with the Applicant should Pancrecarb receive an Approval action during a subsequent review cycle.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1

The CFF Dosing Guidelines (from Borowitz et al., 1995¹²) 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. 2002¹³ 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. 1997¹⁴ 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

¹² 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.

¹³ 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.

¹⁴ 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

Table 12. Complete List of Pancrecarb Clinical Studies

Study No.	Design	Product	Primary Endpoint / Objective	No. of Pts	Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo-controlled, two-way crossover	MS-16 and Placebo	Change in CFA	21	8-43	CF
97-001-1B	Randomized, open-label, active-control two-way crossover	MS-8	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19	12-27	CF
97-001-2	Nonrandomized, open-label, active-control one-way crossover	MS-8	Change in CFA/between usual dose and 50% reduced lipase dose pancrecarb	6	4-17	CF
2001-180	Nonrandomized, open-label, active-control one-way crossover	MS-4	Compare CFA decrease lipase dose by 50%; given by G-tube	6	5-15	CF
092100	Double-blind, randomized, placebo-controlled, two-way crossover	MS-8 and Placebo	Reduction in the frequency of diarrhea	13 [†]	28-55	HIV+ patients [#]
092206	Bioavailability, open-label, placebo-controlled, bioavailability	MS-16 and Placebo Single dose	Demonstrate the intestinal bioavailability of lipase, amylase, and protease from Pancrecarb MS-16	10	36-79	Documented Chronic Pancreatitis*
091897	Nonrandomized, uncontrolled, open-label	MS-8	Weight gain	106	2-42	CF
071503	Nonrandomized, open-label, active-control one-way crossover	MS-16	Difference in mean doses/Determine lowest effective lipase dose	18	12-41	CF
020296 (older formulation [‡])	Double-blind, randomized, active-controlled, 2-way crossover	MS-8 (b) (4)	Differences in CFA between the two treatment periods	22	8-41	CF
111395 (older formulation [‡])	Non-randomized, open-label, active-controlled, 1-way crossover	MS-8 (b) (4)	Differences in CFA between the two treatment periods	10	8-16	CF

*Alcohol-induced chronic pancreatitis or CF

[#]Experiencing HAART induced diarrhea that is successfully managed by pancrelipase therapy.

[†]11 patients completed the study.

[‡] Two clinical studies from 1996 (Studies 020296 and 111395) used an older formulation (b) (4)

(Table above is modified from table found in Clinical Review by Marjorie Dannis.)

2 pages of Appendix 3 have been Withheld in Full immediately following this page as a duplicate copy of Consult Memo dated June 5, 2009 which can be found in Other Reviews of NDA 22222

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22175	----- ORIG 1	----- DIGESTIVE CARE INC	----- PANCRECARB

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
08/27/2009

DONNA J GRIEBEL
08/27/2009

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 27, 2009
FROM: Julie Beitz, MD
SUBJECT: Office Director Memo
TO: NDA 022175 Pancrecarb (pancrelipase) Delayed-Release Capsules
Digestive Care, Inc.

Summary

Pancrecarb (pancrelipase) Delayed-Release Capsules is an exogenous source of porcine-derived pancreatic enzymes. Pancreatic enzyme products (PEPs) serve as replacement therapy for digestive enzymes physiologically secreted by the pancreas and have long been considered the main stay of therapy for exocrine pancreatic insufficiency (EPI). Several PEPs, including Pancrecarb, have been marketed in the US for many years since pre-Drug Efficacy Study Implementation (DESI, pre-1962) and have not undergone review under new drug applications (NDAs).¹ In 2004, to address concerns about variability in potency across products and within product lines, FDA published a Federal Register Notice which stated that PEPs must be marketed under approved NDAs.

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Pancrecarb (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. Before this application may be approved, satisfactory resolution of the identified chemistry, manufacturing, and controls deficiencies for the drug substance (to be addressed by the DMF holder) and for the drug product (to be addressed by Digestive Care, Inc.) will be required. Satisfactory conclusion of discussions regarding the product label and REMS will also be needed.

Dosing

Pancrecarb (pancrelipase) Delayed-Release Capsules is dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Pancrecarb should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. If approved, product labeling will specify dosing recommendations for (b) (4) children 1-4 years of age, and for patients 4 years of age and older. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

Pancrecarb (pancrelipase) Delayed-Release Capsules is not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Pancrecarb, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the U S Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. Thus, if approved, the **Dosage and Administration** section of the Pancrecarb labeling will state that "Pancrecarb is not interchangeable with any other pancrelipase product."

¹ Pancrecarb has been marketed in the US in three strengths, MS-4, MS-8, and MS-16, since 1995, 2000, and 2004, respectively. It is not known whether the currently marketed products differ from the to-be-marketed formulations.

Regulatory History

On October 27, 2008, Digestive Care, Inc. submitted NDA 022175. Inspection of Digestive Care, Inc.'s drug product manufacturing facility on (b) (4) identified numerous deficiencies that were described in a 483 that was issued on (b) (4). Based on these findings, the (b) (4) district compliance branch is considering a recommendation to withhold NDA approval. Satisfactory resolution of these deficiencies is required before this application may be approved.

Concurrent with this review, FDA has reviewed submissions to DMF (b) (4) from the drug substance manufacturer, (b) (4) which supports this NDA. Inspection of (b) (4) or (b) (4) identified numerous deficiencies that were described in a 483 that was issued on (b) (4). Based on these findings, the Office of Compliance has recommended withholding NDA approval. Re-inspection of this facility will be required before NDA 022175 may be approved.²

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, focused on the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Pancrecarb (pancrelipase) Delayed-Release Capsules.

Chemistry, Manufacturing and Controls Considerations

Digestive Care, Inc., (b) (4) formulations of Pancrecarb capsules (b) (4) MS-8, and MS-16 containing (b) (4) 8000, and 16,000 USP units of lipase, respectively. The capsules contain small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase and pancrease). The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5.

(b) (4)

Drug substance. Several deficiencies regarding chemistry, manufacturing, and controls for the drug substance have been identified that preclude approval of the NDA. The (b) (4) facility inspection identified (b) (4) deficiencies that (b) (4) will have to address involving quality systems, production systems, equipment and facilities, laboratory systems and material systems. In addition, several deficiencies were identified in the review of the DMF, including concerns regarding the capacity of the manufacturing process to clear viruses and monitor viral load. These deficiencies will be communicated in a letter from the Division of Therapeutic Proteins to (b) (4).

Drug product. Several deficiencies regarding chemistry, manufacturing, and controls for the drug product have been identified that preclude approval of the NDA. The (b) (4) facility inspection identified (b) (4) deficiencies that Digestive Care, Inc. will have to address, including failure to thoroughly investigate the root cause and identify corrective actions when batches fail, and absent records documenting qualified, approved cleansing procedures for equipment and utensils. In addition, several deficiencies were identified in the review of the NDA involving the applicant's release testing program, stability testing program, process and process validation, acceptance criteria and reference standards, control of excipients, particularly the cellulose acetate phthalate and diethyl phthalate used for (b) (4), a comparison of the currently marketed and to-be-marketed formulations, and discrepancies between manufacturing dates and signature dates on Certificates of Analysis. These deficiencies will be communicated in the complete

² (b) (4) is the also the drug substance manufacturer for Axcan Pharma US, Inc.'s Ultrase MT (pancrelipase) submitted under NDA 022222. The recommendation of the Office of Compliance to withhold NDA approval applies to this NDA as well.

response letter to Digestive Care, Inc.; several of these have been previously conveyed in DGP's July 10, 2009, discipline review letter.

Clinical Pharmacology

Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount. For this reason, a thorough QT assessment for this product has not been requested.

Given the importance of using apple sauce as a means to deliver Pancrecarb microspheres via feeding tubes or to young pediatric patients who cannot swallow capsules, the complete response letter will request that Digestive Care, Inc., repeat the *in vitro* stability study in apple sauce using lipase and amylase assays in which a minimum of five data points are used to assess assay linearity. This request is consistent with other requests made in the letter to enhance analytic methodologies used for lipase and amylase assays.

Efficacy

As with other PEP manufacturers, Digestive Care, Inc., was requested to perform at least one controlled clinical trial with Pancrecarb to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.³ Digestive Care, Inc., conducted two clinical trials.

The short-term safety and efficacy of Pancrecarb MS-16 was evaluated in a single double-blind, placebo-controlled crossover trial in 24 patients, aged 8-43 years (11 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Pancrecarb or placebo for 6-8 days, followed by crossover to the alternate treatment for an additional 6-8 days. All patients consumed a high fat diet. Pancrecarb treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ($p < 0.001$).

A second open-label, active-controlled crossover trial was conducted in 19 cystic fibrosis patients, aged 12-27 years, to determine the short-term safety and efficacy of Pancrecarb MS-8 compared to the patient's usual pancreatic enzyme product (Creon 20, Pancrease MT-10 or MT-20, Ultrase MT-12, MT-18, or MT-20). Treatments were dosed at 50% of the usual lipase dose. The mean coefficient of fat absorption on Pancrecarb was similar to that on usual enzyme therapy. Results from this trial are difficult to interpret because the trial was open-label, had no washout period between the two crossover treatment periods, and permitted repeated stool collections if initial collections were deemed inadequate. In addition, there was no statistical analysis plan prepared during or after the trial, and no missing data handling or multiplicity adjustment strategy. Therefore, DGP recommends, and I concur, that this trial not be relied upon to demonstrate the efficacy or safety of Pancrecarb MS-8.

No clinical trial evaluating the safety and efficacy of Pancrecarb MS-4 was conducted.

(b) (4)

Safety

Delayed and immediate release formulations of porcine-derived PEPs used to treat exocrine pancreatic insufficiency have been generally well tolerated. The most common adverse events reported relate to the

³ See <http://www.fda.gov/cder/guidance/6275f1.htm>

patients' underlying disease and are referable to the gastrointestinal tract. Pancreatic enzyme products are not absorbed from the gastrointestinal tract and are not systemically active.

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of pancreatic enzyme products, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. 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. Patients receiving doses higher 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. If approved, a Medication Guide will be required as part of a REMS for Pancrecarb that will inform patients of this risk.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Pancrecarb is not retained in the mouth. Pancrecarb should not be crushed or chewed or mixed with foods having a pH greater than 4.5 since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Risk of Transmission of Viral Disease to Patients. Like other porcine-derived PEPs, Pancrecarb is derived from porcine pancreas tissue obtained as a by-product from the slaughter of pigs as a source of food. Audit procedures are in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption and to ensure that legal requirements regarding e.g., hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. Two broad categories of porcine viruses, enveloped and non-enveloped viruses, may be transmissible to humans (i.e., have zoonotic potential). In addition, viruses with zoonotic potential such as HEV, the causative agent for hepatitis E, have recently emerged in pigs. The manufacturing process appears to inactivate most enveloped viruses that could be present in the drug substance but has limited capacity to inactivate non-enveloped viruses.

Although there has been no documentation of viral transmission to humans, FDA's Anti-Viral Advisory Committee concluded that there was a theoretical risk of transmission of viral disease to patients treated with porcine-derived PEPs, including Pancrecarb. If approved, a Medication Guide will be required as part of a REMS for Pancrecarb that will inform patients of this theoretical risk. In addition, the applicant will be requested to conduct postmarketing commitments to ensure that the manufacturing process effectively controls viral load.

Risk of Hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing Pancrecarb to patients with gout, renal impairment, or hyperuricemia.

Risk of Severe Allergic Reactions. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported in patients with a known allergy to proteins of porcine origin who are treated with PEPs.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the tradenames (b) (4) "Pancrecarb MS-8", and "Pancrecarb MS-16" are not acceptable. (b) (4)

Pediatric Considerations

Pediatric Use. If approved, the **Use in Special Populations** section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Pancrecarb were demonstrated. In addition, the label will 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.”

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

At the time of approval, FDA will determine the ages of pediatric patients with cystic fibrosis for which Digestive Care, Inc., has fulfilled the pediatric study requirement. FDA will waive the pediatric study requirement for ages 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, and the small number of patients diagnosed in this age category and their geographic dispersal would make conduct of a study in this age group highly impracticable.

At the time of approval, FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight 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.

Postmarketing Requirements under 505(o)

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following serious risks associated with the use of Pancrecarb (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs): the known serious risk of fibrosing colonopathy with higher doses of PEPs and the unexpected serious risk of transmission of viral disease to patients.

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

Therefore, based on appropriate scientific data, FDA has determined that Digestive Care, Inc., is required, pursuant to section 505(o)(3) of the FDCA, 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 Pancrecarb in the US and to assess potential risk factors for the event.
2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancrecarb.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

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 Pancrecarb (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.

Digestive Care Inc.'s proposed REMS, submitted on July 31, 2009, will need to be analogous to REMS for other porcine-derived PEPs, and will consist of a Medication Guide and a timetable for submission of assessments of the REMS. FDA's review of the proposed REMS has been deferred to the next review cycle.

Julie Beitz, MD
Director,
Office of Drug Evaluation III
CDER, FDA

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22175	----- ORIG 1	----- DIGESTIVE CARE INC	----- PANCRECARB

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

/s/

JULIE G BEITZ
08/27/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-175
Submission Code	N
Letter Date	October 27, 2008
Stamp Date	October 27, 2008
PDUFA Goal Date	August 27, 2009
Reviewer Name	Marjorie F. Dannis, MD
Through	Anil Rajpal, MD
Review Completion Date	August 24, 2009
Established Name	Pancrelipase Delayed-Release Capsules
(Proposed) Trade Name	Pancrecarb
Therapeutic Class	Pancreatic Enzyme Product (PEP)
Applicant	Digestive Care, Inc.
Priority Designation	Standard
Formulation	For oral administration
Dosing Regimen	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Indication	Exocrine pancreatic insufficiency
Intended Population	Patients with exocrine pancreatic insufficiency

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends a Complete Response (CR) action based upon manufacturing and product deficiencies.

From a solely clinical perspective, the safety and efficacy of Pancrecarb MS-16 have been established for the treatment of patients with exocrine pancreatic insufficiency (EPI), ages one month to adult. The pivotal study 06-001 demonstrated the short-term efficacy and safety of

Pancrecarb MS-16 for patients with Cystic Fibrosis (CF) and EPI, ages eight years to adult. The Agency has determined that 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. Thus, in the opinion of this Reviewer, the clinical data submitted in the NDA are adequate to label the Pancrecarb MS-16 for patients with EPI from one month through adulthood.

1.2 Risk Benefit Assessment

The efficacy and safety of Pancrecarb MS-16 was demonstrated by the results of one short-term Phase 3 trial (Study 06-001). The pivotal study, 06-001, was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pancrecarb MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of CF and EPI. Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pancrecarb MS-16 and placebo. The results showed that there was a clinically meaningful and statistically significant increase in CFA in Pancrecarb MS-16 treated patients versus patients treated with placebo. In addition, the patients who were the most severely affected (had the lowest placebo CFA level), gained the most benefit by having the largest increase in CFA.

Exposure to Pancrecarb during many of the clinical studies was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. Four deaths occurred during the Pancrecarb development program (all during the 2 year long term study), none of which was thought by investigators or by this Reviewer to be related to the study drug. The few (total of four) Serious Adverse Events (SAEs) were also thought by investigators and this Reviewer not to be related to Pancrecarb treatment. The Adverse Events (AEs) observed during the studies were consistent with the underlying diseases of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. In general, the AE profiles reported in these studies was similar to the side-effect profiles of PEPs as reported in the medical literature.

PEPs are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. Although the clinical development program for Pancrecarb included patients as young as two years of age, the study that incorporated these younger patients (Study 091897) was performed using a different formulation of Pancrecarb (b) (4). In addition, due to the design of this study (nonrandomized, uncontrolled, open label) and a primary endpoint chosen which was not "change in CFA", (b) (4)

(b) (4) The pivotal study, 06-001, was the only study that established the efficacy and safety of Pancrecarb (only the MS-16 formulation) for patients with CF and EPI ages eight years or older.

The Division is not requesting that the Sponsor conduct any additional clinical trials to include patients younger than eight years of age. The Agency has decided that the existence of extensive data from studies in the published literature with a variety of PEP formulations across pediatric

age groups constitutes sufficient evidence of the efficacy for PEPs in the pediatric population. In addition, evidence of efficacy for Pancrecarb MS-16 for patients ages eight to adult was established in the pivotal trial [REDACTED] (b) (4) [REDACTED]. The Sponsor is asked to submit a waiver for the age group of birth to 4 weeks.

Overall, the clinical information obtained from the short-term efficacy and safety studies is adequate to support approval of Pancrecarb MS-16.

1.3 Recommendations for Postmarketing Risk Management Activities

1.3.1 Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

In accordance with section 505-1 of the FDCA, a REMS is necessary for Pancrecarb Delayed-Release Capsules 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.

The proposed REMS must include a **Medication Guide**: and a **Timetable for Submission of Assessments**. The timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. Each assessment must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

1.3.2 Postmarketing Study Requirements (PMRs)

The Agency has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients taking Pancrecarb Delayed-Release Capsules.

Therefore, based on appropriate scientific data, the Agency has determined that, if this application is approved in a subsequent review cycle, pursuant to section 505(o)(3) of the FDCA, The following studies will be required:

1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pancrecarb Delayed-Release Capsules in the US and to assess potential risk factors for the event.
2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancrecarb Delayed-Release Capsules.

The specific details of these required postmarketing studies will be described more fully in the approval letter for this application, should it be approved.

1.3.3 Recommendations for other Postmarketing Study Commitments

Postmarketing Commitments will be negotiated should Pancrecarb receive an approval action during a subsequent review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

Pancrecarb is the investigational agent studied in this application. Pancrecarb is a pancreatic enzyme product for oral administration. The delayed release capsules are bicarbonate-buffered and contain enteric-coated microspheres derived from porcine pancreatic enzymes. The active ingredient pancrelipase is a concentrated porcine extract comprised of the pancreatic enzymes lipase, amylase, and protease. Pancrecarb consists of pancrelipase formulated in (b) (4) dosage strengths: (b) (4) MS-8 (8,000 USP units of lipase), and MS-16 (16,000 USP units of lipase). The enteric coating is designed to facilitate the enzyme delivery into the duodenum.

The proposed trade name for this application is Pancrecarb. This name is currently under review.

The Sponsor is proposing that Pancrecarb receive the following indication:

“Pancrecarb is a pancreatic enzyme preparation indicated for:

Treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF),
(b) (4)

(b) (4)

The following is the Sponsor’s proposed dosing regimen for meals:

- CF-Associated EPI: Begin therapy with 1,000 USP units of lipase/kg of body weight/meal in children less than 4 years of age, 500 lipase units/kg/meal (b) (4) in children 4 years and older, and adjust dosage according to symptoms to less than 2,500 units/kg/meal (b) (4) or less than 4,000 lipase units/g of fat per day. (b) (4)

(b) (4)

(b) (4)

The dosing regimen listed above for CF patients is consistent with the recommendations of the Cystic Fibrosis Foundation (CFF):

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children <4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy. Total daily dose (3 meals plus 2 or 3 snacks) should not exceed 10,000 lipase units/kg/day.¹

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are many PEPs being used in the US to treat EPI in adults and children, including neonates. PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as over-the-counter (OTC) and prescription therapies; however, in the US, PEPs were never evaluated for safety and efficacy under NDA until recently when the FDA required that all PEPs be marketed under an approved NDA by 2010. Cotazym (NDA 20-580) was approved in 1996, but is not currently marketed. On April 30, 2009, Creon (Pancrelipase) was approved (NDA 20-725) for the treatment of EPI due to CF or other conditions. Thus, Creon is the only currently marketed approved PEP.

2.3 Availability of Proposed Active Ingredient in the United States

Previously formulated Pancrecarb is currently marketed in the US and worldwide. The manufacturer does not have specific data on the number of patients treated with Pancrecarb. However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b) (4) Pancrecarb capsules were shipped to wholesalers. If the usual range of daily intake of Pancrecarb is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pancrecarb on an annual basis.

In addition, the active ingredient in Pancrecarb, pancrelipase, is presently widely available from several different manufacturers as enteric coated (EC) and non-EC formulations (which are not

¹ Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46. (PMID: 16782527)

interchangeable). Thus, many different PEP formulations are currently available in the United States and worldwide.

The availability of pancrelipase in the US may change in the near future. Secondary to concerns about variability in potency and safety of PEPs, the FDA is requiring that all PEPs be marketed under an approved NDA by April 28, 2010. Thus, PEPs will no longer be available without a prescription. Please see Section 2.5 for a complete description of regulatory history.

2.4 Important Safety Issues with Consideration to Related Drugs

PEPs were first marketed in the US prior to the Food Drug and Cosmetic Act of 1938; thus, they had never been evaluated for safety and efficacy under an NDA. In the 1990's, concerns about variability in potency and safety (such as fibrosing colonopathy) led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective (GRAS and GRAE, respectively). There were substantial irregularities in potency resulting in patients being both under dosed, as well as over dosed, each presenting a different safety and efficacy concern.

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). Fibrosing colonopathy (FC) is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs.² There was also a concern that the enteric-coating or excipients in the delayed-release PEP formulations could lead to FC. As a result of these potential efficacy and safety concerns, the CFF and FDA published weight-based dosing guidelines for PEP administration (see section 2.1). Thus, monitoring for FC should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products, as should the CFF/FDA weight-based dosing guidelines.

Hyperuricemia and hyperuricosuria have been reported in patients with EPI treated with PEPs. Caution should be exercised when prescribing PEPS to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the initial NDA submission for Pancrecarb. Relevant pre-submission regulatory activity for Pancrecarb was notable for the following:

A Special Protocol Assessment was submitted by the Sponsor on June 20, 2006. The protocol (No. 06-001) was entitled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Crossover Study to Evaluate the Effectiveness and Safety of Pancrecarb MS-16 (pancrelipase) in Reducing Steatorrhea in Children and Adults with Cystic Fibrosis. The Division and the Sponsor reached agreement on:

² FitzSimmons, SC, Burkhardt, GA, Borowitz, D et al. High Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Cystic Fibrosis. New England Journal of Medicine. May 1997; 336 Number 18; 1283-9.

The overall study design of the study which appeared to meet the criteria for demonstrating efficacy and safety set forth in the “Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs.”

The dose stabilization period of 7 to 10 days appeared to be sufficient to qualify the subjects for the study.

The washout period of 7 to 10 days between the double-blind crossover treatment periods appeared to be sufficient in duration to reestablish baseline conditions.

The primary endpoint of comparison between active study drug and placebo in reduction of steatorrhea, as measured by change in percent coefficient of fat absorption (CFA), was acceptable. The CFA was to be calculated from the 72-hour stool collections and dietary records.

The patient population of CF patients was acceptable.

On February 5, 2007, the Division met with the Sponsor to discuss clinical and chemistry and manufacturing issues to satisfy requirements for NDA submission. The Sponsor believed that clinical studies (b) (4)

Therefore, the Agency recommended that the Sponsor perform bioavailability studies with two dosage strengths of Pancrecarb, (b) (4)

Furthermore, if the Sponsor was unable to demonstrate comparability, they would need to provide adequate clinical efficacy and safety data for those strengths that were not shown to be comparable.

The regulatory background of the PEPs is as follows:

PEPs were first marketed in the US in the 1920’s prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as OTC and prescription therapies; however, PEPs had never been evaluated for safety and efficacy under an NDA.

Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule in the Federal Register (FR) on 15-July-1991 establishing that PEPs are not considered GRAS and GRAE, and the PEPs were considered misbranded. Concurrently, the Agency declared its intention to consider all PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on

the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008. In October 2007, enforcement discretion was extended until 28-April-2010, but all PEPs must have an open IND by 28-April-2008, and an NDA submitted by 28-April-2009.

In April 2006, The Guidance for Industry; Exocrine Pancreatic Insufficiency Drug Products was published³ (the Guidance). In this document, the FDA stated its expectation that animal- (porcine- and bovine-) derived PEP NDA applications would be submitted as 505(b)(2) applications. In these submissions, Sponsors were allowed to have a limited clinical development program, which could include short-term studies to establish efficacy and safety. These abbreviated clinical development programs are acceptable for PEP applications because assumptions were made about the efficacy and safety of these drugs based on a large body of efficacy and safety information available in the medical literature. The PEPs are also considered to be the standard of care for EPI due to CF and other causes, as described in the current CFF consensus statement.

2.6 Other Relevant Background Information

PEPs are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. Although the clinical development program for Pancrecarb included patients as young as two years of age, the study that incorporated these younger patients (Study 091897) was performed using a different formulation of Pancrecarb (b) (4). In addition, due to the design of this study (nonrandomized, uncontrolled, open label) and a primary endpoint chosen which was not “change in CFA”, the results obtained were not sufficient to support the efficacy of the Pancrecarb MS-8 formulation. The pivotal study, 06-001, was the only study that established the efficacy and safety of Pancrecarb (only the MS-16 formulation) for patients with CF and EPI ages eight years or older.

The Division is not requesting that the Sponsor conduct any additional clinical trials to include patients younger than the age of eight. The Agency has decided that the existence of extensive data from studies in the published literature with a variety of PEP formulations across pediatric age groups constitutes sufficient evidence of the efficacy for PEPs in the entire pediatric population.

In addition, during a teleconference with the Sponsor on June 24, 2009, the Division stated that each of the (b) (4) Pancrecarb formulations differ from one another such that comparability of the (b) (4) formulations relative to one another had not been shown by the information provided in the NDA submission. Furthermore, additional clinical studies may be required to approve the (b) (4) MS-8 strengths. (b) (4)

³ 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.pdf>). April 2006.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

DSI inspections of selected clinical sites were performed, and included the inspection of Sites 007 in Cleveland, Ohio and 191 in Iowa City, Iowa (Drs. Strausbaugh and Ahrens respectively). These sites were selected by the Division based on the number of patients enrolled (Site 007 had 6 patients; Site 191 had 5 patients). In addition, Site 007 had the highest mean change in the coefficient of fat absorption (%CFA) and the highest number of treatment responders. The recommendation by DSI Investigator Roy Blay, Ph.D. is that “the data generated by the clinical sites of Drs. Strausbaugh and Ahrens appear acceptable in support of the respective application”.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. The Sponsor, Digestive Care Inc., states that they did not enter into a financial agreement with any of the clinical investigators which would affect the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC data have been extensively reviewed by the Drug Product and Drug Substance Reviewers. A Complete Response Action is recommended. The Drug Product review states, “The data submitted in this application do not support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. Issues that preclude approval of this application include inadequate release and stability testing, inadequate process validation and inadequate stability data to support an assignment of expiry.” Please see the CMC reviews for more detailed information.

4.2 Clinical Microbiology

According to Microbiology Reviewer, Vinayak Pawar, Ph.D., the drug product is a solid oral dosage form with microbial limit specifications and no microbiology deficiencies preventing approval which were identified. The reviewer did have the following comment to the Sponsor:

“USP Chapter <1111> and the methods provided in Chapters <61> and <62> have been revised as of May 1, 2009. The acceptable limits for nonaqueous preparations for oral use are as follows:

- Total Aerobic Microbial count = 10^3 CFU/g or mL which translates to a maximum acceptable count of 2000 CFUs.
- Total acceptable combined yeast/molds count = 10^2 CFU/g or mL or 200 CFUs.
- Absence of *Escherichia coli*.

We recommend that you update your microbial limits requirement to the revised USP specifications.”

Thus, NDA 22-175 was recommended for approval on the basis of a satisfactory product quality microbiology review. Please see the Microbiology Review for more detailed information on the microbiology data.

(b) (4) is the Drug Substance manufacturer for the Drug Product, Pancrecarb. A facility inspection took place during (b) (4) and revealed microbial contamination which could potentially be of clinical significance, especially to a chronically ill patient population such as CF patients. A consultation with Dr. Lorenz (Infectious Disease specialist of The Division of Anti-infective and Ophthalmology Products) revealed that although several types of microorganisms were present in the Drug Substance, these organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans. Thus, their presence may not necessarily constitute a significant risk for most immunocompetent individuals. Dr. Lorenz recommended that since manufacturing levels exist for these particular organisms, the appropriate measures should be instituted to rectify the

contamination. In addition, he recommended the testing of the final product for microbial and toxin contamination; however, later discussion revealed that this would not be possible.

4.3 Preclinical Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, and consistent with recommendations in the Guidance, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. As outlined in the FDA Guidance for exocrine pancreatic insufficiency products, no toxicology studies were needed if excipients were classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. The sponsor did not conduct any nonclinical studies with Pancrecarb. All of the excipients used in Pancrecarb were USP/NF compendial items, and some were also GRAS and/or present at levels previously found to be acceptable. Please see the Nonclinical Pharmacology Review (by Tamal K. Chakraborti, Ph.D.) for more detailed information on the nonclinical information relevant to this NDA submission.

4.4 Clinical Pharmacology

Clinical pharmacology data have been reviewed by the Clinical Pharmacology Reviewer, PeiFan Bai, Ph.D. Her recommendation, from a clinical pharmacology perspective, is that the Pancrecarb application has the following deficiency:

“The submitted applesauce study (Protocol #080705) is deemed unacceptable since the assay method was not adequately validated. Therefore, we recommend that the sponsor repeat the applesauce study with a newly validated analytical method based on CMC’s recommendation (a minimum of 5 data points for determination of assay linearity), and submit the results of the repeated applesauce study to FDA for review. The recommendation in the labeling with regard to the use of applesauce as a mixing medium to facilitate administration will be based on the review outcome. If the sponsor chooses not to repeat the applesauce stability study, there will be no recommendations with regard to the use of applesauce in the labeling.”

Of note is that according to the ongoing internal discussions of DPG, the bioavailability study using the intubation procedure is now considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum.

Please see Clinical Pharmacology Review for complete details.

4.4.1 Mechanism of Action

Pancrecarb acts locally in the gastrointestinal (GI) tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed.

4.4.2 Pharmacodynamics

Lipase, amylase, and protease act locally in the GI tract and are not systemically absorbed; therefore, pharmacodynamic studies are not applicable.

4.4.3 Pharmacokinetics

PEPs act locally in the GI tract and are not absorbed; therefore, pharmacokinetic studies are not applicable.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

There were a total of ten clinical studies (including one bioavailability) conducted in the Pancrecarb clinical development program; these clinical studies included a number of different designs (e.g., randomized, placebo-controlled, active-controlled, crossover, open-label). Duration of treatment in the trials also varied; the duration of treatment ranged from 7 days up to 2 years. The total number of patients enrolled in each study ranged from 6 to 106. See Table 1 for a listing and summary of these studies.

Table 1: Clinical Studies for Pancrecarb

Study Number	Design	Product	Primary Endpoint/Objective	No. of Pts / Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo controlled, 2-way crossover	MS-16 and placebo	Change in CFA	21/ 8-43	CF
97-001-1B	Randomized, open-label, active controlled, 2-way cross-over	MS-8	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19/ 12-27	CF
091897	Nonrandomized, uncontrolled, open label	MS-8	Weight gain	106/ 2-42	CF
97-001-2	Nonrandomized, open label, active controlled 1-way cross-over	MS-8	Change in CFA between usual dose and 50% reduced lipase dose Pancrecarb	6/ 4-17	CF
092100	Double blind, randomized, placebo -controlled, 2-way crossover	MS-8 and Placebo	Reduction in the frequency of diarrhea	13/ 28-55	HIV+ patients*
071503	Nonrandomized, open label, active controlled, 1-way cross-over	MS-16	Difference in mean doses/Determine lowest effective lipase dose	18/ 12-41	CF
2001-180	Nonrandomized, open label, active controlled, 1-way cross-over	MS-4	Compare CFA decrease lipase dose by 50% Given by G-tube	6/ 5-15	CF
092206	Open-label, placebo-controlled, bioavailability	MS-16 and placebo	Demonstrate the intestinal bioavailability of lipase, amylase and protease from MS-16 (single dose)	10 subjects enrolled Ages 36-79 years	Chronic Pancreatitis [#]
020296 (Study from 1996 with older formulation)	Double-blind, randomized, active-controlled, 2-way crossover	MS-8 low bicarbonate	Differences in CFA between the two treatment periods	22/ 8-41	CF
111395 (Study from 1996 with older formulation)	Non-randomized, open-label, active-controlled, 1-way crossover	MS-8 low bicarbonate	Differences in CFA between the two treatment periods	10/ 8-16	CF

* Experiencing HAART induced diarrhea that is successfully managed by pancrelipase therapy

Documented alcohol-induced chronic pancreatitis or CF

5.2 Review Strategy

There were ten studies submitted with this NDA. They include one bioavailability study, two controlled clinical studies, one uncontrolled clinical study, and six supportive clinical studies. This review focuses on the two controlled clinical studies: the pivotal study (06-001) and study 97-001-1B. In addition, separate efficacy analyses were done for Study 97-001-2 (non-randomized, open label, active controlled, 1-way cross-over study using MS-8 formulation) and Study 2001-180 (nonrandomized, open label, active controlled, 1-way cross-over study using MS-4 formulation). There were two clinical studies (020296 and 111395) that were performed

using an older formulation of Pancrecarb. With the exception of inclusion in the general safety sections, the two studies with different formulations were not reviewed.

The majority of time was spent reviewing the pivotal study, 06-001. Efficacy of the MS-16 formulation of Pancrecarb was established from this randomized, double-blind, placebo-controlled study. Study 97-001-1B was a randomized, open-label, active-controlled, 2-way crossover study. The comparison between MS-8 and the reference pancreatic enzymes, at approximately 50% of their required dosages, failed to show superiority of Pancrecarb in improving CFA.

A pooled safety analysis was performed on all of the studies. Additionally, safety was assessed separately for Study 06-001 and Study 97-001-1B.

This NDA was submitted as a 505(b)(2) application. To obtain approval, PEP NDAs must meet the requirements for clinical studies described in 21 CFR 314.50. The Agency determined that there was a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis (69 FR 23410). Thus, the limited clinical development program of Pancrecarb (one small pivotal study) was acceptable. However, the pivotal study used exclusively the MS-16 dosage strength and neither of the other two dosage strengths was adequately investigated. Thus, only the efficacy of Pancrecarb MS-16 was established.

5.3 Discussion of Individual Studies

5.3.1 Study 06-001

5.3.1.1 Study Design

The pivotal study, 06-001 was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pancrecarb MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI). Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pancrecarb MS-16 and placebo. The study was conducted between February 13, 2007 and September 4, 2007.

The study consisted of 6 periods defined as: Screening Period which included a Screening Visit (Day -14 to -10), Dose Stabilization Period (-10 to 0 days), Treatment Period 1 (Days 1 and 2 at home; Days 3 to 6 in the General Clinical Research Center [GCRC]), Washout/Re-Stabilization Period (7 to 10 days), Treatment Period 2 (Days 1 and 2 at home, Days 3 to 6 in the GCRC) and the Follow-up Period which included End of the Study Visit (14 days following discharge at the end of Treatment Period 2)

Figure 1: Overall Study Design

- Screening Period
 - 4 days: Determine eligibility
- Open-label Dose Titration/Stabilization Period
 - 7-10 days: Pancrecarb
- **Treatment Period 1**
 - **6-8 days: Pancrecarb or Placebo**
- Washout/Re-stabilization Period
 - 7-10 days: Pancrecarb
- **Treatment Period 2**
 - **6-8 days: Pancrecarb or Placebo**
- Follow-up Period
 - 14 days after end of Treatment Period 2

5.3.1.2 Study Objectives

The primary objective of the study was to determine the efficacy and safety of Pancrecarb MS-16 versus placebo in reducing steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with CF and EPI.

5.3.1.3 Patient Population

5.3.1.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females seven years of age and older, and:

- Had confirmed diagnoses of CF – One or more clinical features consistent with CF *and* genotype consistent with CF or sweat chloride concentration > 60 mEq/L, and
- Had confirmed diagnosis of EPI - Currently receiving treatment with another PEP and documented fecal elastase < 100 micrograms/g stool.

5.3.1.3.2 Key Exclusion Criteria:

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of fibrosing colonopathy.
- History of solid organ transplant or major bowel surgery.
- History of being refractory to pancreatic enzyme replacement therapy (PERT)
- Had a condition known to increase fecal fat loss including: inflammatory bowel disease, celiac disease, Crohn's disease, tropical Sprue, Whipple's disease
- Had a current diagnosis or a history of distal intestinal obstruction syndrome (DIOS) in the past 6 months, or 2 or more episodes of DIOS in the past 12 months
- Poorly controlled diabetes or recent illness involving acute systemic administration of antibiotics within previous two weeks

5.3.1.4 Concomitant Medications

Patients were allowed to continue all usual CF medications and treatments, chronic oral azithromycin therapy, and inhaled antibiotic therapy. Study subjects could remain on a chronic regimen of systemic (oral or IV) antibiotics (except erythromycin) if they started the antibiotics at least 2 weeks prior to study screening, were at their usual bowel pattern at the time of screening, and did not stop or change these antibiotics during the study period.

Concomitant administration of the following medications was prohibited during the study: drugs or products that affect fat absorption, including enemas, all laxatives including natural products (with exception of bisacodyl if required and prescribed by the investigator at any time during the study), mineral oil and castor oil, olestra (fat substitute), all fat blocking nutritional supplements, gastrointestinal motility modifiers, barium, potassium chloride, calcium carbonate, magnesium hydroxide, and enzymatic supplements.

5.3.1.5 Study Visits and Procedures

The majority of study visits were in the outpatient setting (study Visits 1, 2, 4, 6). During Visits 3 and 5, patients were hospitalized for four to six days wherein they were fed a controlled diet and were monitored. The two, 72-hour stool collections were performed during the inpatient stays for Visits 3 and 5. The study visits and procedures are summarized in Table 2 (electronically copied and reproduced from the Sponsor's submission).

Table 2: Schedule of Study Assessments

	SCREENING PERIOD		TREATMENT PERIOD 1						WASHOUT- RE-STABILIZATION PERIOD 7-10 DAYS	TREATMENT PERIOD 2						FOLLOW- UP PERIOD END OF STUDY VISIT 6 DAY 14±3		
	SCREENING VISIT 1 DAY -14 TO -10	DOSE STABILIZATION PERIOD DAYS -10 TO 0	VISIT 2 D0	IN-HOME		IN-HOSPITAL - VISIT 3				VISIT 4 D0	IN-HOME		IN-HOSPITAL - VISIT 5					
				D1	D2	D3	D4	D5			D6 [-2]	D1	D2	D3	D4		D5	D6 [-2]
Informed consent	X																	
Medical history	X																	
Complete physical exam	X					X							X				X	
Abbreviated physical exam			X							X								
Height (cm)	X																	
Weight (kg)	X		X			X	X	X	X	X			X	X	X	X	X	
Vital signs	X		X			X	X	X	X	X			X	X	X	X	X	
Oximetry	X																	
Spirometry	X																	
Hematology	X								X								X (X) [†]	
Chemistry	X								X								X (X) [†]	
Urinalysis	X								X								X (X) [†]	
Spot urine (for uric acid / creatinine)	X								X							X	(X) [†]	
Pregnancy test (urine)	X ^a		X ^a							X ^a								
Review of Inc/Exc Criteria	X		X ^a															
FE-1 test	X ^c																	

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Table 2: Schedule of Study Assessments (cont.)

	SCREENING PERIOD		TREATMENT PERIOD 1						WASHOUT/ RE-STABILIZATION PERIOD 7-10 DAYS	TREATMENT PERIOD 2						FOLLOW- UP PERIOD END OF STUDY VISIT 6 DAY 14+3		
	SCREENING VISIT 1 DAY -14 TO -10	DOSE STABILIZATION PERIOD DAYS -10 TO 0	VISIT 2 D 0	IN-HOME		IN-HOSPITAL - VISIT 3				VISIT 4 D 0	IN-HOME		IN-HOSPITAL - VISIT 5					
				D1	D2	D3	D4	D5			D6 [+2]	D1	D2	D3	D4		D5	D6 [+2]
Study subject diaries ^d		X	X	X	X				X	X	X	X						
Dietitian and RC instruction	X	X																
Phone follow-up		X		X	X				X		X	X						
High-fat diet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Open-labeled PANCRECARB [®] MS-16		X	X					X ^b	X	X						X ^c	X	
Randomization			X															
Treatment Periods 1 and 2 active study drug or placebo				X	X	X	X	X	X ^e		X	X	X	X	X	X	X ^e	
Admit to GCRC						X	X	X	X				X	X	X	X		
Administer dye marker						X			X ^f				X			X ^f		
72-hour stool collection						X	X	X	X				X	X	X	X		
Food records						X	X	X	X				X	X	X	X		

	SCREENING PERIOD		TREATMENT PERIOD 1						WASHOUT/ RE-STABILIZATION PERIOD 7-10 DAYS	TREATMENT PERIOD 2						FOLLOW- UP PERIOD END OF STUDY VISIT 6 DAY 14+3		
	SCREENING VISIT 1 DAY -14 TO -10	DOSE STABILIZATION PERIOD DAYS -10 TO 0	VISIT 2 D 0	IN-HOME		IN-HOSPITAL - VISIT 3				VISIT 4 D 0	IN-HOME		IN-HOSPITAL - VISIT 5					
				D1	D2	D3	D4	D5			D6 [+2]	D1	D2	D3	D4		D5	D6 [+2]
Stool characteristics and frequency recording						X	X	X	X					X	X	X	X	
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

^a For women of childbearing potential.

^b Review of Inclusion/Exclusion Criteria (confirmed that the results of fecal elastase test met Inclusion Criteria).

^c Fecal elastase performed on random stool sample.

^d Diary was completed by study subject or parent (in the case of a minor) during the in-home portions of the study.

^e Discontinued after the breakfast dose.

^f If the first dye marker was not passed before the second dye marker was to be administered, the second dye marker was administered 96 hours after the first dye marker (Day 7).

^g Repeated if results at the end of Treatment Period 2 were abnormal and clinically significant.

^h Start previously established dose of PANCRECARB[®] MS-16 at the beginning of lunch.

ⁱ Start previously established dose of PANCRECARB[®] MS-16 or the subject's routine standard of care pancreatic enzyme treatment and usual diet at the beginning of lunch.

5.3.1.6 Randomization and Controls

The randomization was performed according to the (b) (4), which described the generation of kit identifiers, emergency unblinding envelopes, and the kit distribution list. (b) (4) prepared a randomization list linking kit number to treatment sequence. Unblinded personnel in the DCI drug packaging group printed and applied the kit labels. Kit labels did not include any information that would reveal whether drug supplied for each treatment period was Pancrecarb MS-16 or placebo. Kit identifiers were prepared for the 2 age groups, ≥7 to 17 years and 18 years and older. As the patients enrolled into the study, the Clinical Project Manager assigned the next available kit from the appropriate age group of the kit distribution list.

Study drug (active study drug or placebo) for Treatment Period 1 and Treatment Period 2 was labeled with double-blinded investigational agent labeling. The label listed the name and address of the sponsor, protocol number, product storage information, a statement that it was “Active Study Drug or Matching Placebo”, the required FDA investigational agent warning statement, a kit number and a bottle number. Each bottle was labeled with the treatment period for which it was to be used. Each bottle had a space for the study pharmacist or study coordinator to write in the study subject number and the date it was dispensed. Each bottle of study drug had 100 capsules of either active study drug or the matching placebo. All study site personnel were blinded to which product was used in each treatment period.

Enrollment of Additional Subjects

Twenty-nine subjects were enrolled in order to complete 20 evaluable subjects: 10 subjects ≥ 7 to 17 years of age (children) and 10 patients ≥ 18 years of age (adults). Patients who failed screening or who were randomized but withdrew prior to completion of Treatment Period 2 were replaced with a new subject.

In response to the Agency’s Information Request (IR) regarding subject discontinuations, the sponsor clarified that three subjects discontinued and then two were enrolled as new patients following study screening and randomization procedures. Included in that response, the sponsor also indicated that there were three patients who had food intake records corrected after the database lock, which affected the primary efficacy assessments. The sponsor should have spontaneously informed the Agency regarding these details; however, the efficacy conclusion that Pancrecarb MS-16 increased CFA levels was still upheld.

The randomization was performed according to the [REDACTED] ^{(b) (4)}, which described the generation of kit identifiers, emergency unblinding envelopes, and the kit distribution list. [REDACTED] ^{(b) (4)} prepared a randomization list linking kit number to treatment sequence. Unblinded personnel in the DCI drug packaging group printed and applied the kit labels. Kit labels did not include any information that would reveal whether drug supplied for each treatment period was Pancrecarb MS-16 or placebo. Kit identifiers were prepared for the 2 age groups, 7 to 17 years and 18 years and older. As the subjects enrolled into the study, the Clinical Project Manager assigned the next available kit from the appropriate age group of the kit distribution list. The DCI drug supply group then shipped the kit and emergency unblinding information to the study site.

5.3.1.7 Study Medication Dose Selection, Dispensing, and Compliance

The dose for each subject was selected during the Dose Stabilization Period. During this time period, a high-fat diet (approximately 2 gm fat/kg/day) was consumed. The patient’s Pancrecarb MS-16 dose was managed in order to achieve control of pancreatic insufficiency symptoms and to achieve stabilized status according to the clinician’s observations and subject’s signs and symptoms. This chosen dose was used during the subsequent treatment periods.

Doses in this study were not to exceed a maximum lipase dose of 2500 lipase units/kg/meal, which is in agreement with the recommendation in the Guidance for Industry (FDA, 2006) of titration to less than 2500 lipase units/kg/meal.

Active study drug: Enteric-coated microspheres of pancrelipase, encapsulated in opaque gelatin capsules to mask its identity.

Placebo: Enteric-coated microspheres containing sodium starch glycolate and sucrose in place of pancrelipase, encapsulated in opaque gelatin capsules to mask identity.

Patients took all doses of study drug by mouth at the beginning of meals and snacks. The dose established during the Dose Stabilization Period was the dose used for the remainder of the study during Treatment Periods 1 and 2, and the Washout/Re-Stabilization Period.

An accurate and current accounting of the dispensing and return of study drug for each study patient was maintained on an ongoing basis by a research pharmacist. The amount of study drug dispensed and returned by the study subject was recorded on the Investigational Project Accountability Record. The study monitors verified these documents throughout the course of the study.

5.3.1.8 Efficacy and Endpoint Measures

5.3.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb versus placebo. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool collection) during the efficacy evaluation period of each double-blind treatment period. Food intake was strictly controlled and recorded for 72 hours by qualified site personnel. The fecal fat measurements were obtained during a 72-hour in hospital stool collection. CFA was calculated as:

$$\frac{\text{fat intake} - \text{fat excretion}}{\text{fat intake}} \times 100$$

The per-protocol population consisted of all study subjects who were randomized and completed both treatment periods with adequate 72-hour stool collections for analysis, with no major dosing protocol violations.

5.3.1.8.2 Secondary Endpoints

1. The coefficient of nitrogen absorption (CNA)
2. Stool frequency (number of bowel movements)
3. Stool weight

5.3.1.8.3 Safety Endpoints

Safety endpoints included assessments of or changes in frequency, duration, and severity of treatment-emergent AEs, clinical laboratory parameters, physical examination findings, and vital sign measurements in the safety population. The safety analysis population was defined as all patients who were randomized and received at least one dose of study drug.

5.3.1.9 Statistical Considerations

The primary endpoint comparison of CFA observed during treatment with placebo and during treatment with Pancrecarb was done using an analysis of variance appropriate for the crossover design. A *t* test for two independent samples was used to calculate power and sample size. An estimate of within-patient variance for calculating the effect size was not available; thus, the between-patient pooled variance was used instead.

According to Statistical reviewer, Freda W. Cooner, Ph.D.:

“The sample size was estimated based on mean treatment effect size of 30% in CFA difference between placebo and pancreatic enzyme and standard deviation of 41.2. The sponsor used normal approximation formula $N = (Z_{\alpha} + Z_{\beta})^2 \times (41.2)^2 / (30\%)^2$, where $Z_{\alpha} = 1.96$ for 2-sided significance level of 0.05 and $Z_{\beta} = 1.28$ for 90% of power, to determine that 20 subjects were required for the primary comparison. According to the protocol (dated October 23, 2006), enrollment of 24 subjects would be sufficient to result in 20 evaluable subjects with 10 in each age group. However, as the result of subject discontinuations, it became necessary to enroll more than 24 subjects in order to complete 20 evaluable subjects. Therefore, the sponsor later indicated in the SAP (dated September 5, 2007) that “[t]he planned enrollment was up to 30 male or female subjects in order to complete 20 evaluable subjects...”

5.3.1.10 Protocol Amendments

According to the Sponsor, there were no amendments made to the protocol (dated 23 October 2006) or the Statistical Analysis Plan (SAP; dated 05 September 2007).

5.3.1.11 Study Results

5.3.1.11.1 Demographics

There were 29 patients between the ages of 8 and 43 years enrolled in Study 06-001. The mean age in children (≥ 7 to 17 years) was 12 years and in adults (≥ 18 years), 27 years. More males than females were enrolled in both age groups (children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. The demographics of patients enrolled in Study 06-001 are summarized below in Table 3.

Table 3: Demographics of Study 06-001

	Children < 18 (n=11)	Adults ≥ 18 (n=13)	Overall (n=24)
Age (years)			
Mean (SD)	12 (2.9)	27(7.4)	20(9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

5.3.1.11.2 Patient Disposition

Twenty-nine patients were enrolled in the Study 06-001. Of these 29 patients, 5 discontinued prior to randomization (screen failures) and 24 were randomized. Three patients discontinued the study (2 due to AEs and 1 protocol violation) and 21 subjects completed the study. A summary of patient disposition by age group is presented in Table 4 below.

Table 4: Patient Disposition

	Children n (%)	Adults n (%)	Overall n (%)
Enrolled	14 (100%)	15 (100%)	29 (100%)
Randomized *	11 (79%)	13 (87%)	24 (83%)
Completed Study	10 (71%)	11 (73%)	21 (72%)
Discontinued Study After Randomization	1 (7%)	2 (13%)	3 (10%)
Adverse Event	1 (7%)	1 (7%)	2 (7%)
Protocol Violation	0 (0%)	1 (7%)	1 (3%)
Per Protocol	9 (64%)	10 (67%)	19 (66%)

* Note: Patient took at least one dose study drug

There were five study sites with between four and nine patients enrolled at each site. Enrollment by site is summarized in Table 5.

Table 5: Patients per Study Site

Site Number	007	009	184	191	195
	007004	009004	184001	191005	195002
	007003	009003	184002	191004	195004
	007002	009001	184004	191003	195001
	007006	009002	184003	191002	195003
	007010	009006		191001	
	007001	009005		191006	
	007005				
	007009				
	007008				
Total Patients	9	6	4	6	4

5.3.1.11.3 Concomitant Medications

All study patients were to be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. All concomitant medication and concurrent therapies were documented at the Screening Visit and at all study visits and at early termination when applicable. Dose, route, frequency of administration, and indication for administration, and dates of medication were captured.

5.3.1.11.4 Compliance with Study Medication

An accurate and current accounting of the dispensing and return of study drug for each study subject was maintained on an ongoing basis by a research pharmacist. The amount of study drug dispensed and returned by the study subject was recorded on the Investigational Project Accountability Record. The study monitors verified these documents throughout the course of the study.

Patient compliance with the study drug was determined in each of the two efficacy evaluation periods (Study Visit 2 and Study Visit 4) based on the review of the patient diary. Additionally, the study coordinator was in telephone contact with the patient on a daily basis to follow up with the patient on the high-fat diet compliance, active study drug or placebo compliance, and any AEs. At study's completion, the data obtained from patient diaries and from the research pharmacist were reconciled.

5.3.1.11.5 Dosing Information/Exposure

During the open-label Titration/Stabilization period and the open label Dose Re-stabilization Period 1, the mean dosage of study drug was approximately 1406 lipase units/kg/meal and 1557 lipase units/kg/meal respectively. Dosages were similar during both the double- blind treatment periods with a mean dose of 1565 lipase units/kg/meal.

One patient (184-002) had lipase doses over the protocol-specified maximum lipase dose of 2500 lipase units/kg/meal (Dose Stabilization 2799 lipase units/kg/meal; Wash-out/Re-Stabilization 2783 lipase units/kg/meal; and Double-blind treatment period 2720 lipase

units/kg/meal). At the Screening Visit, this subject’s regimen was 88,000 lipase units/day consisting of 4 capsules of 20,000 lipase units and 1 capsule of 8,000 lipase units. Because this study only supplied the Pancrecarb MS-16 strength (16,000 units of lipase/capsule), if any rounding of doses was needed, the study subject was to be administered a lower starting dose. In error, the site rounded up and placed the subject on a 6 capsule/meal regimen, equivalent to 96,000 lipase units and 2720 lipase units/kg/meal, instead of 5 capsules/meal, equivalent to 80,000 lipase units, and 2266 lipase units/kg/meal. Despite the administration of this slightly (10%) higher than recommended dose, no gastrointestinal AEs were reported for this subject.

5.3.1.11.6 Protocol Deviations and Violations

A total of 33 protocol deviations occurred during this study. Two patients with deviations/violations were excluded from the Per Protocol analysis population, and one patient was excluded from the Completed Treatment analysis population. The protocol deviation/violations assessed by the Sponsor as major are tabulated below in Table 6.

Table 6: Major Protocol Deviation/Violations

Subject Number	Type of Deviation/Violation	Explanation	Timing of Deviation/Violation
009-003	Inclusion/Exclusion Criteria	Did not fulfill Exclusion Criteria, (abdominal surgery within the past 5 years). Had gastrostomy tube surgically removed secondary to excessive leak. A waiver was granted.	Prior to Screen Failure
195-001	Inclusion/Exclusion Criteria	Began dosing in Treatment Period 1 before the FE-1 results were available and Inclusion Criteria No. 4 confirmed (pancreatic insufficiency documented by spot FE-1 \leq 100 μ g/g stool at the time of randomization).	At Randomization
009-002	Dosing	Prior to confirmation of eligibility, the subject took dose of open-label drug in error. He returned the study drug to the site.	Prior to Screen Failure
184-002	Dosing	Received lipase doses over the protocol-specified maximum lipase dose of 2500 lipase units/kg/meal.	Post-Randomization Excluded from PP Population
191-002	Dosing	Given double-blinded drug instead of open-label drug at lunch at the GCRC at the end of Treatment Period 1. At discharge, the subject received the open-label study drug per protocol. Received 2 times the intended dose of double-blind medication at lunch on 2 occasions during Treatment Period 2.	Post-Randomization Excluded from PP population
191-005	Efficacy	Discarded part of the 72-hour stool collection in Treatment Period 1 (placebo).	Post-Randomization Excluded from PP population

5.3.1.11.7 Efficacy Results

5.3.1.11.7.1 Primary Efficacy Analysis

The primary endpoint in Study 06-001 was the change in the CFA in the efficacy population. The CFA measured during treatment with Pancrecarb was compared with the CFA measured

during treatment with placebo. Twenty-one patients who completed both double-blind treatment periods were included in the efficacy analysis population.

The Sponsor's results show that the mean CFA for patients receiving Pancrecarb was 82.5%; the mean CFA for patients receiving placebo (no treatment) was 46.3%. Therefore, the mean change in CFA was 36.2%. The efficacy results show a mean change in CFA that was statistically significant ($p < 0.001$). The FDA Statistician confirmed the results and was in agreement with the Sponsor. The results are summarized in Table 7 (electronically copied and reproduced from the Sponsor's submission).

Table 7: Comparison of Percent Coefficient of Fat Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162 ^a	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007 ^a	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317 ^a	25.848, 48.786

^a $P < 0.001$

Source: 06-001 Study Report (Page 48, Section 11.1.1, Table 11-1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with Pancrecarb as compared to patients on placebo (no treatment). In the Pancrecarb clinical development program, the primary endpoint results were analyzed in conjunction with the changes in CFA for individual patients (see Section 5.3.1.11.6.2 below)

5.3.1.11.7.2 Additional Analyses of the Primary Endpoint

This Reviewer performed additional analyses of the primary endpoint, including analyses of the change in CFA by no-treatment (placebo) CFA, by treatment sequence, by gender, and by age.

Analysis by No-Treatment CFA

A widely accepted definition of severe EPI is patients who have a CFA less than or equal to 40% on no treatment. In addition, treatment effect has been reported to be more pronounced in patients with lower no-treatment CFA. The medical literature notes that in the most severely affected patients an increase from baseline in CFA of 30% represents a clinically meaningful change, thus, this subgroup of patients was analyzed separately.

There were nine patients in the severe category. They had a mean placebo (no-treatment) CFA of 27% and a mean change in CFA on Pancrecarb of 51%. All but one of the most severely affected patients had an increase in CFA greater than or equal to 45%. Patient 195003 had an increase in CFA of 20%. This Reviewer looked for reasons to explain the apparent decreased efficacy for this particular patient relative to the other severely affected patients; however, no etiology was identified. Thus, in general, the most severely affected patients demonstrated the

greatest response to treatment with Pancrecarb. The magnitude of the change (mean change 51% in this group, and $\geq 45\%$ in most of the patients) was a clinically meaningful result. Individual results for patients with CFA <40 on placebo are tabulated below in Table 8.

Table 8: Patients with Placebo CFA <40

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
009001	19	85	66
007002	19	71	52
007008	21	65	45
195003	24	44	20
195004	27	88	61
184003	30	92	62
007005	31	90	59
007001	36	82	46
191002	37	84	47

Mean change CFA (for Placebo CFA <40 subgroup) = 51

For the subgroup of patients who had mild or moderate EPI (N=12) (defined by this Reviewer as a no-treatment CFA greater than 40), the mean change in CFA was 26%. The increase in CFA following Pancrecarb treatment (mean change in CFA of 26) was not as pronounced as seen in the patients with severe EPI. This result is not unexpected as these moderately affected patients have less of a capacity to respond, since they started at a higher no-treatment level. Individual results for patients with CFA <40 on placebo are tabulated below in Table 9. In general, there was a gradation in treatment responses with larger increases in CFA for patients with placebo CFAs at the low end, and smaller increases for higher placebo CFA levels.

Table 9: Patients with Placebo CFA >40

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
191006	42	81	39
191004	48	78	30
195002	52	76	24
195001	52	90	38
184001	58	93	35
007010	58	91	33
007009	59	86	27
184004	63	97	34
009006	69	89	20
191003	71	79	8
184002	74	85	11
191001	78	90	12

Mean change CFA (for Placebo CFA >40 subgroup) = 26

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA in Study 06-001 showed that the increase in CFA on Pancrecarb treatment is greatest in the most severely

affected patients. The patients who had a higher no-treatment CFA showed smaller increases in CFA after treatment with Pancrecarb.

The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. The mean change in CFA for all patients with a placebo CFA<40 was 51%; All of the patients (except patient 195003) who were the most severely affected (placebo CFA<40) gained the most benefit by having had an increase in CFA of at least 45%. This percentage increase was defined by the medical literature as a clinically meaningful result. Most other patients also had increases in CFA following treatment with Pancrecarb.

These results above support the approval of Pancrecarb for the treatment of EPI; treatment with Pancrecarb is beneficial to most patients. The treatment effect is variable; however, it follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

Analysis by Treatment Sequence

The efficacy results were analyzed according to sequence. Patients in sequence AB were randomized to receive Pancrecarb during the first treatment period followed by placebo during the cross-over treatment period. There were slightly more patients randomized to the AB sequence as opposed to the BA sequence (12 in sequence AB; 9 in sequence BA). The mean change in CFA was similar for patients in each sequence, 39% for sequence AB and 33% for sequence BA. The Statistical Reviewer also analyzed the efficacy results according to sequence and did not note any visible impact on efficacy outcomes. See Tables 10 and 11.

Table 10: Sequence AB Patients

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
195003	24	44	20
195004	27	88	61
184003	30	92	62
007005	31	90	59
007001	36	82	46
191002	37	84	47
191006	42	81	39
195001	52	90	38
184001	58	93	35
007010	58	91	33
009006	70	90	20
191003	71	79	8
Mean	45	84	39

Table 11: Sequence BA Patients

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
009001	19	85	66
007002	19	71	52
007008	21	65	45
191004	48	78	30
195002	52	76	24
007009	59	86	27
184004	63	97	34
184002	74	85	11
191001	78	90	12
Mean	48	81	33

The above analysis supports the fact that the order of treatment (placebo to Pancrecarb or Pancrecarb to placebo) did not affect the efficacy of Pancrecarb.

Analysis by Gender and Age

The efficacy results were also analyzed by gender and by age. The mean change in CFA was 39 in males vs. 29 in females; however, it was difficult to assess mean changes in CFA with respect to gender as there were three times as many males in the study as females (six females were included in the efficacy analysis population).

There were no meaningful differences in mean change in CFA with respect to age. A comparison between treatments within each age group (children vs. adults) was made and the results were similar to the overall analysis observed for both children and adults.

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb versus placebo. The overall results showed that a clinically meaningful and statistically significant increase in CFA was demonstrated in the efficacy analysis population, with an overall mean change in CFA of 36% (p <0.001; 95% CI [-31.7, -19.3]). Unplanned additional and subgroup analyses showed that factors such as treatment sequence, gender, and age did not appear to affect efficacy; however, patients with lower placebo-treatment CFA tended to have a better response to treatment with Pancrecarb.

As expected from the published medical literature with treatment with other PEPs, the patients in this study who were the most severely affected (with the exception of one patient) gained the most benefit by having had an increase in CFA of at least 45%: this percentage increase was defined by the medical literature as a clinically meaningful result. Conversely, patients with higher placebo CFA had a lesser responses to Pancrecarb treatment.

5.3.1.11.7.3 Secondary Efficacy Analysis

There were several secondary efficacy endpoints in this study. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; (b) (4)

(b) (4) The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Coefficient of Nitrogen Absorption (CNA)

A major secondary endpoint was the comparison of CNA after administration of Pancrecarb versus placebo.

The results showed that the mean CNA for Pancrecarb and placebo were 79% and 47%, respectively. The mean change in CNA was 32%, and this was a statistically significant change. (See Table 12 electronically scanned and copied from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 12: Comparison of Percent Coefficient of Nitrogen Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	78.986	47.169	31.817 ^a	26.102, 37.533
Children (n = 10)	78.440	43.810	34.630 ^a	26.365, 42.895
Adults (n = 11)	79.532	50.528	29.005 ^a	21.183, 36.826

^a P<0.001

Source: 06-001 Study Report (Page 49, Section 11.1.1.2.1, Table11-3)

These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

Stool Frequency

Another secondary endpoint was the comparison of stool frequency (number of bowel movements) between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool frequency was 6.1 bowel movements/72 hours for Pancrecarb versus 10.1 for placebo treatment. The difference of 4, a 39.6% decrease in stool frequency with Pancrecarb compared to placebo treatment was statistically significant (P<0.001). (See Table 13 electronically scanned and copied from Sponsor)

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Table 13: Comparison of Stool Frequency (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	6.086	10.089	-4.004 ^a	-5.607, -2.400
Children (n = 10)	5.591	9.409	-3.817 ^b	-6.136, -1.499
Adults (n = 11)	6.580	10.770	-4.190 ^a	-6.384, -1.995

^aP <0.001, ^b P=0.003

Source: 06-001 Study Report (Page 50, Section 11.1.1.2.2, Table11-5)

Although statistically significant, the clinical significance of a four bowel movement difference over a 72 hour period is not clear.

Stool Weight

Another secondary endpoint was the comparison of stool weight between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool weight was 655.9 g/72 hours for Pancrecarb versus 1308.5 for placebo treatment. The difference of a 652.6 gram decrease in stool weight with Pancrecarb compared to placebo treatment, was statistically significant (P<0.001). (See Table 14 electronically scanned and copied from Sponsor)

Table 14: Comparison of Stool Weight (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	655.939	1308.524	-652.585 ^a	-813.369, -491.801
Children (n = 10)	507.129	1086.246	-579.117 ^a	-811.610, -346.624
Adults (n = 11)	804.748	1530.802	-726.053 ^a	-946.082, -506.024

^aP <0.001

Source: 06-001 Study Report (Page 51, Section 11.1.1.2.3, Table11-7)

Once again, the clinical significance of a 653 gram difference in stool weight over a 72 hour period is not clear.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. Most secondary endpoints were subjective and assessed without using validated endpoint measures. Study 06-001 was of short duration and had a disproportionate amount of Pancrecarb treatment time, which made the analysis of treatment differences more difficult.

(b) (4)

5.3.1.11.8 Review of Safety

5.3.1.11.8.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths reported during Study 06-001. There was one serious adverse event (SAE) reported by one patient, as follows:

Patient 184-002 was a 10-year-old Caucasian female who experienced an SAE of CF (verbatim term: acute exacerbation of CF) at the follow-up visit (Day 14) at the end of Treatment Period 2. The patient received Pancrecarb during Treatment Period 2. The SAE was treated with concomitant medication, although no new concomitant medication was prescribed. The SAE was assessed as resolved at an unscheduled visit to follow the SAE.

This event was assessed by the investigator to be probably secondary to the patient's underlying disease of Cystic Fibrosis, and was not attributed to treatment with study medication. This Reviewer is in agreement with the investigators' assessment.

5.3.1.11.8.2 Common Adverse Events

Of the 24 subjects randomized, 21 (87.5%) patients reported a total of 112 treatment-emergent adverse events (TEAEs). During Pancrecarb MS-16 treatment, 16 patients reported 47 TEAEs and during placebo treatment, 17 subjects reported 65 TEAEs. Ten of the 21 subjects reported TEAEs during both treatments.

There were no obvious differences in the types of AEs reported during either treatment period. The most commonly reported AEs were in the gastrointestinal and respiratory systems as would be expected in this patient population. The most commonly reported AEs were abdominal pain, flatulence, abdominal distension, and headache. Two patients discontinued the study secondary to AE's; both patients were receiving placebo during this time. Patient 007-006 discontinued secondary to weight loss and patient 009-005 discontinued secondary to hyperglycemia and elevated liver function tests. One patient experienced an SAE (preferred term: CF; verbatim term: acute exacerbation of CF). The patient was receiving Pancrecarb MS-16 treatment when the SAE occurred.

Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature. See Table 15 below for a complete listing of the AEs reported in this study, (i.e., reported by 1 or more patients; $\geq 4\%$ of patients).

Table 15: Study 06-001, AEs observed during Treatment Period and Crossover Treatment Period

System Organ Class	Preferred Term	Pancrecarb MS-16 N=21 (%)	Placebo N=24 (%)
Gastrointestinal disorders	Abdominal distension	2 (10)	4 (20)
	Abdominal pain	7 (33)	9 (38)
	Abnormal feces	1 (5)	0
	Constipation	0	0
	Diarrhea	2(10)	1 (4)
	Dyspepsia	2(10)	1(4)
	Flatulence	2(10)	5 (21)
	Frequent bowel movements	0	1 (4)
	Gastro esophageal reflux disease	1(5)	0
	Mouth hemorrhage	1(5)	0
	Nausea	1(5)	1 (4)
	Rectal tenesmus	0	1(4)
	Toothache	1(5)	0
	Vomiting	1(5)	2 (8)
Respiratory, thoracic and mediastinal disorders	Cough	2(10)	1(4)
	Nasal congestion	1(5)	2 (8)
	Pharyngeal erythema	1(5)	1(4)
	Pharyngo-laryngeal pain	1(5)	2 (8)
	Productive cough	0	1(4)
	Rales	1(5)	1(4)
	Rhinitis allergic	1(5)	0
	Sneezing	0	0
	Wheezing	1(5)	0
Nervous system disorders	Dizziness	0	1(4)
	Headache	2(10)	3 (13)
Investigations	Alanine aminotransferase increased	0	1(4)
	Aspartate aminotransferase increased	0	1(4)
	Blood glucose increased	0	1(4)
	Gamma-glutamyltransferase increased	0	1(4)
	Hemoglobin urine present	1(5)	0
	Sputum abnormal	0	1(4)
	Weight decreased	1(5)	2 (8)
Musculoskeletal and connective tissue disorders	Arthralgia	1(5)	0
	Back pain	1(5)	0
	Bone pain	0	1(4)
	Myalgia	0	1(4)
	Pain in extremity	0	1(4)
General disorders and administration site conditions	Chest pain	0	1(4)
	Pyrexia	0	1(4)
Hepatobiliary disorders	Hepatic steatosis	0	1(4)
Infections and infestations	Cellulitis	1(5)	0
Injury, poisoning and procedural complications	Thermal burn	0	0
Metabolism and nutrition disorders	Hypoglycemia	1(5)	0
Psychiatric disorders	Sleep disorder	0	0

Skin and subcutaneous tissue disorders	Rash	1(5)	0
	Urticaria	0	0
Surgical and medical procedures	Nasal sinus drainage	0	0
Vascular disorders	Hot flush	0	1(4)
Congenital, familial and genetic disorders	Cystic fibrosis	1(5)	0

5.3.1.11.8.3 Safety Summary

Exposure to Pancrecarb MS-16 (with average doses of about 1500 lipase units/kg/meal) during the study was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. There were no deaths during Study 06-001 and the one SAE reported during the study (exacerbation of CF) was assessed by the investigator to be related to the patient's underlying disease (CF). Two patients discontinued from the study due to AEs: one patient had weight loss and one patient had elevated LFT's. The weight loss was resolved at the follow-up visit; the LFT's were still mildly elevated at the follow-up visit. There were no other clinically significant abnormalities in laboratory data; individual patient vital signs and physical exams remained stable throughout the study.

The AEs observed during Study 06-001 were consistent with the underlying disease of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. The most commonly reported AEs were abdominal pain, flatulence, abdominal distension, and headache. Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature.

5.3.1.12 Summary and Conclusions for Study 06-001

The primary endpoint of the pivotal study, 06-001, was met. Treatment with Pancrecarb resulted in a statistically significant increase in absorption of fat (increase in CFA) compared to placebo. The most severely affected patients (placebo CFA <40%) demonstrated the greatest response to treatment with Pancrecarb (mean increase in CFA equal to 51), which was clinically meaningful. Subgroup analyses showed that factors such as treatment sequence and age did not appear to affect efficacy. The efficacy of Pancrecarb was demonstrated in adults and pediatric patients eight years or older.

Exposure to Pancrecarb during the study was within the range of what is currently encountered for PEP treatment of CF patients in clinical practice. The safety profile of Pancrecarb was acceptable and was consistent with the safety profile reported for other PEPs.

Thus overall, the results of the pivotal trial demonstrate that CF patients who are treated with Pancrecarb MS-16 have objective and subjective improvement of their clinical symptoms of EPI, and that Pancrecarb MS-16 is reasonably well tolerated by this patient population. These results support the approval of Pancrecarb MS-16 for the treatment of EPI in this patient population.

5.3.2 Study 97-001-B

5.3.2.1 Study Design

The supportive study, 97-001-1B, was a multicenter, randomized, open-label, active-controlled, two-way crossover study evaluating the efficacy and safety of Pancrecarb MS-8. This study, in 19 patients with a confirmed diagnosis of CF and EPI, was designed to compare measures of fat malabsorption before (while on usual PEP treatment) and after oral administration of Pancrecarb MS-8 at ~50% reduced lipase dose.

The study was carried out during two consecutive seven-day treatment periods in patients with CF. The dosage of Pancrecarb MS-8, the test pancreatic enzyme and the reference pancreatic enzymes [Creon[®] 20 (Solvay Pharmaceutical); Pancrease[®] MT-10 and MT-20 (Ortho/McNeil); Ultrase[®] MT-12, MT-18, and MT-20 (Axcan/Scandipharm)] were to be adjusted to ~50% of each patient's routine lipase dose requirement, but not lower than ~1,800 USP Units of lipase per gram of fat intake per day.

At the time of the screening visit, all patients were to have received pancreatic enzyme therapy in the form of Creon[®], Pancrease[®], or Ultrase[®]. The patients were then instructed to record their daily dietary intake and collect stools for three days on their regular enzyme dose. After determination of the current lipase dose, the existing enzyme therapy dose was reduced by ~50%, but not lower than ~1800 units of lipase per gram of fat intake per day. These reduced lipase doses were maintained throughout the study during each seven day treatment arm of the study. Following the first stool collection, the patients were instructed to collect stools for an additional three days on their reduced lipase dose. Only those patients with a coefficient of fecal fat excretion of no less than 15% (equivalent to CFA no more than 85%) during the initial ~50% reduced enzyme dose were randomly assigned in the two crossover treatment periods.

There were no wash-out periods between each of the two treatment periods; thus, patients remained on some PEP for the duration of the study.

5.3.2.2 Study Objectives

The objectives of this study were to determine the safety and efficacy of Pancrecarb at ~50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with cystic fibrosis when compared to other PEPs.

5.3.2.3 Patient Population

5.3.2.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females greater than six years of age and:

- Had confirmed diagnoses of CF established by duplicate sweat chloride measurements greater than 60 mEq/L, using the method of Gibson and Cooke
- A coefficient of fecal fat excretion of $\geq 15\%$ in the second outpatient stool collection using $\sim 50\%$ of usual enzyme dose

5.3.2.3.2 Key Exclusion Criteria

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of meconium ileus requiring surgical bowel resection.
- Receiving oral antibiotics or any drug known to interfere with fat digestion
- Participation in another concurrent clinical trial known to interfere with gastrointestinal motility and absorption of nutrients
- Patient is refractory to exogenous enzyme supplementation.

5.3.2.4 Concomitant Medications

It was the responsibility of the investigator to ensure that all changes in medication, or the commencement of medication during the study, were recorded in full in the case report form in a manner corresponding to the entries in the patient's medical records.

5.3.2.5 Study Visits and Procedures

The study visits and procedures are outlined below (electronically copied and reproduced from the sponsor's submission).

Days 1-3 (Home)

The following were recorded:

1. Drug Treatment
2. Food Records
3. Stool Description (number, consistency)
4. Adverse Events
5. Concomitant Medication

Days 4-7 General Clinical Research Center (GCRC)

Patients entered the GCRC the evening of the third day and were discharged after passing the second stool marker, usually on Day 7.

The following were recorded:

1. Drug Treatment
2. Weighing and Recording of Food Intake as outlined in Food Records
3. Stool Collection for Fecal Fat and Nitrogen using markers
4. Stool Description (number, consistency)
5. Adverse Events
6. Concomitant Medication
7. Nutritional Assessment

At the time of discharge, patients returned all unused medication and were dispensed the alternate enzyme product for Treatment Period 2.

Days 8-10 (Home)

1. Drug Treatment
2. Food Records
3. Stool Description (number, consistency)
4. Adverse Events
5. Concomitant Medication

Days 10-14 (GCRC)

Patients entered the GCRC the evening of Day 10 and were discharged after passing the second stool marker, usually on Day 14.

1. Drug Treatment
2. Determination of Fecal Fat and Nitrogen using markers
3. Weighing and Recording of Food Intake
4. Stool Description (number, consistency)
5. Physical Examination (Day 14)
6. Adverse Events
7. Concomitant Medication
8. Nutritional Assessment

5.3.2.6 Randomization and Controls

This study was a randomized, open-label, active-controlled, two-way crossover study. Patients were randomly assigned in the two crossover treatment period to receive either their usual enzyme dose at ~50% decrease lipase dose or Pancrecarb MS-8 at ~50% decreased lipase dose. No blinding procedures were used during the study.

5.3.2.7 Study Medication Dose Selection, Dispensing, and Compliance

At the time of the screening visit, all patients were to have received pancreatic enzyme therapy in the form of Pancrease, Creon, or Ultrase. After determination of the current lipase dose, the existing enzyme therapy dose was reduced by ~50%, but not lower than ~1800 units of lipase per gram of fat intake per day.

Only those patients with a coefficient of fecal fat excretion of $\geq 15\%$ during the ~50% reduced enzyme dose (second stool collection) were admitted in the subsequent two treatment periods. Patients were then assigned randomly to one of two cross-over treatment sequences. The reduced lipase doses were maintained throughout the study on each seven-day treatment arm of the study. The patients either received a seven day supply of Pancrecarb or their usual pancrelipase product in the form of Pancrease, Creon, or Ultrase. A seven-day supply of enzyme capsules were dispensed and accounted for during the study period.

The investigator was to maintain accurate records of receipt of all test articles, including dates of receipt. In addition, records were kept regarding when and how much of each test article was dispensed to and used by each individual patient in the study. Reasons for departure from the expected dispensing regimen were recorded. A Drug Dispensing Form was provided for this

purpose. At the conclusion of the study, quantities of drug were reconciled with the dispensing documents, and the remaining drug was returned to the sponsor for accounting and disposition.

5.3.2.8 Efficacy and Endpoint Measures

The protocol did not identify any analysis population, yet two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site.

5.3.2.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb at ~50% reduced lipase dose as compared to usual PEP at ~50% reduced lipase dose. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool collection) during the efficacy evaluation period of each treatment period. The fecal fat measurements were obtained during a 72-hour in hospital stool collection. CFA was calculated as:

$$\frac{\text{fat intake} - \text{fat excretion}}{\text{fat intake}} \times 100$$

5.3.2.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint was the percent of nitrogen malabsorption (CNA).

5.3.2.9 Statistical Considerations

As per Statistical Reviewer;

“There was no SAP during or after the clinical study. The final protocol specified that the primary outcome of percentage fat excreted would be compared between Pancrecarb MS-8 and the patient’s usual EC enzyme using Grizzle’s method for analyzing crossover studies. It is unclear what the sponsor meant by this Grizzle’s method. Later in the study report, the sponsor indicated that a repeated measure ANOVA was used to assess treatment differences for each primary and secondary outcome variable and daily diary safety variables. The model was adjusted for study center, treatment period, treatment sequence, subject nested within sequence, and study center by treatment interaction. The sponsor further specified that PROC MIXED was used in SAS and treatment by center interaction term was removed due to its insignificance. With no missing data handling or multiplicity adjustment strategies proposed, the sponsor claimed that all variables were assessed at the two-sided 0.05 alpha level.”

5.3.2.10 Protocol Amendments

Most of the protocol amendments were minor and did not impact the review, thus they will not be discussed.

5.3.2.11 Study Results

5.3.2.11.1 Patient Disposition, Demographic and Baseline Characteristics

Study 97-001-1B was conducted over approximately a four-year period from March 1997 to August 2001. Twenty-seven patients (Cincinnati site, 16; Indianapolis site, 11) were screened for study enrollment. Of the 27 patients, seven patients did not meet entry criteria and 20 patients (Cincinnati, 9; Indianapolis 11) were enrolled and randomized to treatment in the study. One patient (007) in the Cincinnati study center did not participate in the second arm treatment and was excluded from the efficacy analysis; thus 19 patients completed all study visits.

One patient from each site was enrolled with CFA greater than 85% and they were still included in the analyses. During the study, the investigators were allowed to repeat treatment assessments based on their judgments of whether a given treatment phase met protocol requirements. In three patients (002, 003, and 009) at the Cincinnati site, the investigators felt the Carmine red stool dye marker failed because of its color and so each had a repeat stool collection at their second treatment period. Two patients (004 and 009) at the Indianapolis site had repeat studies as outpatients based on the investigator's assessment of inadequacy of stool collections or possible lab error in specimen handling. The sponsor decided these repeat studies were not considered major protocol deviations although such a provision (i.e., to repeat studies based on the investigator's assessment that stool collection results are spurious) was not specified in the final protocol. One patient (011) at the Indianapolis site was non-compliant with the protocol specified diet and was identified by the sponsor as a major protocol violation.

While the protocol did not identify any analysis population, two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site. The demographic variables are summarized in Table 16 below.

Table 16: Summary of Baseline Demographics (ITT Population)

	Cincinnati (n = 8)	Indianapolis (n = 11)	Overall^a (n = 19)
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6
Weight (kg)			
Mean (SD)	52.8 (10.0)	58.6 (12.5)	56.2 (11.6)
Min – Max	37.0 – 69.9	29.8 – 82.3	29.8 – 82.3
Height (cm)			
Mean (SD)	159.9 (7.4)	163.8 (12.6)	162.2 (10.7)
Min – Max	148.2 – 172.0	135.8 – 182.0	135.8 – 182.0

^a The results concur with those from the sponsor
 Source: Statistical Reviewer’s Table

5.3.2.11.2 *Efficacy Results*

5.3.2.11.2.1 Primary Efficacy Analysis

The following populations are defined for the purposes of the efficacy analysis:

- Intent-to-Treat (ITT) Population: defined as all patients randomized to the study and who completed both treatment phases.
- Per Protocol (PP) Population: defined as all patients that were randomized and completed the study without major protocol deviations. This analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site and 004 and 009 at the Indianapolis site and excluding patient 011 at the Indianapolis site.

The ITT results, listed below in Table 17, showed [REDACTED] (b) (4)

The Sponsor also used a PP population which showed [REDACTED] (b) (4)

Table 17: Efficacy Results

	PANCRECARB[®] MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CFA (%)			(b) (4)
PP Population (n=18) CFA (%)			

Source: Adapted from Statistical Reviewer's Table (the results concur with those from the sponsor)

This reviewer performed an analysis of each individual's response to change in treatment (from Pancrecarb to placebo or vice versa). These results are shown below in Table 18, which represents the ITT population and Table 19, which represents the PP population. When analyzing the individual patient results, (b) (4)

Clinically, an individual patient may have improved symptoms of malabsorption (diarrhea, abdominal pain, flatulence) with increasing CFA values.

Table 18: Efficacy Results (CFA) Study 97-001-1B (ITT population)
(b) (4)

Table 19: Efficacy Results (CFA) Study 97-001-1B (PP population)

(b) (4)



The outcomes for the two populations were vastly different; statistical significance could be shown in the PP population but not the ITT population.

According to the statistical reviewer, this study lacked clinical trial rigidity; it was open-label, there was no washout period between two crossover treatment periods, there were repeated treatment assessments, there was a change of analysis plan, etc. Therefore, the efficacy results were not reliable to support any efficacy claims.

In addition, in each individual patient, the changes in CFA were not clinically meaningful. It is difficult to determine the clinical significance of CFA values that differ by ^{(b) (4)}. In conclusion, Study 97-001-1B was not sufficient to show the efficacy of Pancrecarb MS-8.

5.3.2.11.2.2 Additional Efficacy Analysis

Due to the poor study design and lack of clinical trial rigidity in Study 97-001-1B, no further efficacy analyses were performed.

5.3.2.11.2.3 Secondary Efficacy Analysis

The secondary efficacy endpoint was the comparison of CNA after administration of Pancrecarb MS-8 versus usual enzyme treatment.

In the ITT population, the results showed (b) (4)

In addition, since the clinical significance of CNA is not established, these secondary efficacy results are not clinically meaningful. (See Table 20 electronically scanned and adapted from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 20: Secondary Efficacy Results

	PANCRECARB[®] MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CNA (%)	(b) (4)		
PP Population (n=18) CNA (%)	(b) (4)		

5.3.2.11.2.4 Efficacy Conclusions

While the supportive study, 97-001-1B, did not identify any analysis population, two populations were used for analysis in the study report, an ITT and PP population. The primary efficacy analyses for these two populations were vastly different; the ITT outcome was statistically significant, while the PP outcome was not. In addition, the individual changes in CFA observed per patient were not clinically meaningful.

According to the Statistical Reviewer, “Study 97-001-1B was an open-label, active-controlled, two-way crossover study without washout period and failed to show superiority of MS-8 in increasing CFA compared to the reference pancreatic enzymes, at approximately 50% of their required dosages. This study also had the potential for considerable bias because of inadequate trial design; thus the results were not sufficient to support an efficacy claim.”

In conclusion, the efficacy of Pancrecarb MS-8 was not sufficiently demonstrated in Study 97-001-1B.

5.3.2.11.3 Safety Results

5.3.2.11.3.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths, serious adverse events or other significant AEs reported in Study 97-001-1B.

5.3.2.11.3.2 Common Adverse Events

During this open label, crossover study, 19 patients were randomized and received pre-determined doses of each study medication for 7 days as per protocol. Four patients received Pancrecarb MS-8 during a second 7 day period due to repeating the treatment phase. The mean doses of Pancrecarb MS-8 and usual enzyme taken during the study were both approximately 4,200 lipase units/kg/day.

During Study 97-001-1B, gastrointestinal signs and symptoms were recorded separately in patient diaries as opposed to collected as adverse events. The gastrointestinal signs and symptoms showed no significant differences in abdominal cramping/discomfort, bloating severity, flatulence/gas production severity and overall severity between the two treatments. (See Table 21 electronically scanned and copied from Sponsor.)

Table 21: Diary Data* (Mean ± SD) - ITT

	PANCRECARB® (n = 19)	Usual Pancrelipase (n = 19)
Number of Stools/Day	1.60 ± 0.5	1.43 ± 0.4
Abdominal Cramping/Discomfort	0.34 ± 0.4	0.24 ± 0.4
Bloating Severity	0.13 ± 0.3	0.22 ± 0.4
Flatulence/Gas Production Severity	0.27 ± 0.4	0.31 ± 0.4
Overall Severity	0.32 ± 0.4	0.31 ± 0.4

* None of the differences were statistically significant

With many of the complaints in the gastrointestinal category recorded separately from the other adverse events, there were not many adverse events recorded during Study 97-001-1B. Headache was the only adverse event which occurred in more than one person, 16 % in the Pancrecarb group and 21 % in the usual pancrelipase group. See Table 22 below for incidences of all AEs.

Table 22: Study 97-001-1B Summary of Adverse Events

Adverse Event	Pancrecarb n = 19 (%)	Usual Pancrelipase n = 19 (%)
Headache	3 (16)	4 (21)
Abdominal pain	1 (5)	0
Cold symptoms	1 (5)	0
Constipation	0	1 (5)
Increased sinuses congestion	1 (5)	0
Menstrual cramps	0	1 (5)
Rash	1 (5)	0
Stuffy nose	1 (5)	0
Temp >37.5	1 (5)	1 (5)
Tooth extraction	1 (5)	0

5.3.2.11.3.3 Safety Summary

Exposure to Pancrecarb (with dosages of approximately 4,200 lipase units/kg/day) during the study was similar (although may be slightly less) to what is currently encountered for PEP treatment in CF patients in clinical practice. There were no deaths, serious adverse events or other significant AEs reported in Study 97-001- 1B. There were no cases of fibrosing colonopathy. The only laboratory evaluation performed was fecal fat and fecal nitrogen analyses in stool samples.

Patients reported abdominal discomfort/distension, bloating and flatulence with equal severity in the Pancrecarb and usual pancrelipase treatment groups. These complaints are typical for this patient population of CF patients with EPI. Individual patient vital signs and physical exams remained stable throughout the study.

Therefore, treatment with Pancrecarb appeared to be well tolerated. The safety profile was consistent with that of other PEPs reported in the literature. However, the open-label study design may have introduced bias in the study, so the specific safety information (although minimal) attained from Study 97-001-1B may not be reliable data.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor is proposing that Pancrecarb receive the following indication:

Pancrecarb is a pancreatic enzyme preparation indicated for:

- Treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF),

(b) (4)

Since this application is recommended to receive a CR action, specific wording for labeling of Pancrecarb was not negotiated during this review cycle; however, in the opinion of this Reviewer, the data submitted to the Pancrecarb application support the general statement that Pancrecarb is indicated for the treatment of (b) (4) EPI secondary to a variety of causes, including CF (b) (4). It is noted that all of the patients enrolled in the clinical studies submitted to the NDA had EPI due to cystic fibrosis, except one study which had a population of HIV+ (Human Immunodeficiency virus) patients with HAART induced diarrhea.

(b) (4)

6.1.1 Methods

The efficacy evaluation of the Pancrecarb clinical program involved review of several studies. The pivotal study, 06-001, submitted for this NDA used only the MS-16 dosage strength during the clinical trial. Since the other dosage strengths ((b) (4) MS-8) were not shown to be comparable to the MS-16 dosage strength, this reviewer also reviewed the efficacy data from several supportive clinical trials. These were Study 97-001-2 (a nonrandomized, open label, active controlled, 1-way, cross-over study of 50% decreased dose of MS-8) and Study 2001-180 (nonrandomized, open label, active controlled, 1-way, cross-over study using MS-4 given by gastrostomy tube at 50% decreased dose). The studies will be discussed separately as the differences in study design do not allow for the pooling of data. The two controlled clinical studies 06-001 and 97-001B are reviewed in detail (see Section 5.3 for a detailed review of each of these studies).

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, 06-001, as reasonable and appropriate.

6.1.2 Demographics

The entire clinical development plan for Pancrecarb included patients ages two years to adulthood; however, some of the studies with younger pediatric patients were not robust enough for conclusions to be drawn regarding efficacy and safety based only on those studies.

6.1.2.1 Pivotal Study: 06-001

There were 29 patients between the ages of 8 and 43 years enrolled in Study 06-001. The mean age of children (≥ 7 to 17 years) was 12 years and the mean age of adults (≥ 18 years) was 27 years. More males than females were enrolled in both age groups (children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. Since CF is a disease predominantly of

Caucasians, the study population is representative of the CF population. The demographics of patients enrolled in Study 06-001 are summarized below in Table 23.

Table 23: Demographics of Study 06-001

	Children < 18 (n=11)	Adults ≥ 18 (n=13)	Overall (n=24)
Age (years)			
Mean (SD)	12 (2.9)	27 (7.4)	20 (9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

6.1.2.2 Study 97-001-1B

There were 19 patients between the ages of 12 and 28 years enrolled in Study 97-001-1B. The mean age was 18 years; there were approximately equal numbers of males and females. Once again, the patients were mostly homogeneous in terms of race with the majority of patients being Caucasian, which is representative of the CF population. The demographics of patients enrolled in Study 97-001-1B are summarized below in Table 24.

Table 24: Summary of Baseline Demographics (ITT Population)

	Cincinnati (n = 8)	Indianapolis (n = 11)	Overall^a (n = 19)
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6

^a The results concur with those from the Sponsor
 Source: Adapted from Statistical Reviewer's Table

6.1.3 Patient Disposition

6.1.3.1 Pivotal Study 06-001

Twenty-nine patients were enrolled in the Study 06-001. Of these 29 patients, 5 discontinued prior to randomization (screen failures) and 24 were randomized. Three patients discontinued the study (2 due to AEs and 1 protocol violation) and 21 patients completed the study. A summary of patient disposition by age group is presented in Table 25 below.

Table 25: Study 06-001 Patient Disposition

	Children n (%)	Adults n (%)	Overall n (%)
Enrolled	14 (100%)	15 (100%)	29 (100%)
Randomized *	11 (79%)	13 (87%)	24 (83%)
Completed Study	10 (71%)	11 (73%)	21 (72%)
Discontinued Study After Randomization	1 (7%)	2 (13%)	3 (10%)
Adverse Event	1 (7%)	1 (7%)	2 (7%)
Protocol Violation	0 (0%)	1 (7%)	1 (3%)
Per Protocol	9 (64%)	10 (67%)	19 (66%)

* Note: Patient took at least one dose study drug

There were five study sites with between four and nine patients enrolled at each site. Enrollment by site is summarized in Table 26.

Table 26: Study 06-001 Patients per Study Site

Site Number	007	009	184	191	195
	007004	009004	184001	191005	195002
	007003	009003	184002	191004	195004
	007002	009001	184004	191003	195001
	007006	009002	184003	191002	195003
	007010	009006		191001	
	007001	009005		191006	
	007005				
	007009				
	007008				
Total Patients	9	6	4	6	4

6.1.3.2 Study 97-001-1B

Study 97-001-1B was conducted over approximately a four-year period from March 1997 to August 2001. Twenty-seven patients (Cincinnati site, 16; Indianapolis site, 11) were screened for study enrollment. Of the 27 patients, seven patients did not meet entry criteria and 20 patients (Cincinnati, 9; Indianapolis 11) were enrolled and randomized to treatment in the study. One patient (007) in the Cincinnati study center did not participate in the second arm treatment and was excluded from the efficacy analysis; thus 19 patients completed all study visits.

One patient from each site was enrolled with CFA greater than 85% and they were still included in the analyses. During the study, the investigators were allowed to repeat treatment assessments based on their judgments whether a given treatment phase met protocol requirements. In three patients (002, 003, and 009) at the Cincinnati site, the investigators felt the Carmine red stool dye marker failed because of its color and so each had a repeat stool collection at their second treatment period. Two patients (004 and 009) at the Indianapolis site had repeat studies as outpatients based on the investigators assessment of inadequacy of stool collections or possible lab error in specimen handling. The sponsor decided these repeat studies were not considered major protocol deviations although such a provision (i.e., to repeat studies based on the investigator's assessment that stool collection results are spurious) was not specified in the final protocol. One patient (011) at the Indianapolis site was non-compliant with the protocol specified diet and was identified by the sponsor as a major protocol violation.

While the protocol did not identify any analysis population, two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for 06-001 was to compare the coefficient of fat absorption (CFA) following oral administration of Pancrecarb and placebo or the "change in CFA". The fecal fat measurements were obtained during a 72-hour in-hospital stool collection. The pre-specified mean change in CFA of 28.6% was considered to be statistically significant by the Sponsor.

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and

chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency’s “Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs”, the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, 06-001, as reasonable and appropriate.

The Sponsor’s results show that the mean CFA for patients receiving Pancrecarb was 83%; the mean CFA for patients receiving placebo (no treatment) was 46%. Therefore, the mean change in CFA was 36%. The efficacy results show a mean change in CFA that was statistically significant ($p < 0.001$; 95% CI [28, 45]). The FDA Statistician confirmed the results and was in agreement with the Sponsor. The results are summarized in Table 27 (electronically copied and reproduced from the Sponsor’s submission).

Table 27: Comparison of Percent Coefficient of Fat Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162 ^a	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007 ^a	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317 ^a	25.848, 48.786

^a $P < 0.001$

Source: 06-001 Study Report (Page 48, Section 11.1.1, Table 11-1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with Pancrecarb as compared to patients on placebo (no treatment). The clinical significance of a mean change in CFA of 36% is challenging to interpret as this is an average of all of the patients, regardless of their placebo CFA values. Thus, the primary endpoint results should be examined in conjunction with the changes in CFA for individual patients. This was performed as a subgroup analysis by this Reviewer (see section 5.3.1.11.6.2 above).

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA showed that the increase in CFA on Pancrecarb treatment is greatest in the most severely affected patients. For patients (n=9) with a placebo-treatment CFA <40%, the mean increase in CFA on Pancrecarb treatment was 51%, which is a clinically meaningful increase in CFA. The patients who had a higher no-treatment CFA ($\geq 40\%$ during placebo treatment) showed smaller increases in CFA after treatment with Pancrecarb. The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. These results support the approval of Pancrecarb for the treatment of EPI; treatment with Pancrecarb is beneficial to most patients. The treatment affect is variable; however, it

follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

For Study 97-001-1B, the following populations are defined for the purposes of the efficacy analysis:

- Intent-to-Treat (ITT) Population: defined as all patients randomized to the study and who completed both treatment phases.
- Per Protocol (PP) Population: defined as all patients that were randomized and completed the study without major protocol deviations. This analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site and 004 and 009 at the Indianapolis site and excluding patient 011 at the Indianapolis site.

The ITT results, listed below in Table 28, showed [REDACTED] (b) (4)

The Sponsor also used a PP population which showed [REDACTED] (b) (4)

Table 28: Efficacy Results Study 97-001-1B

	Pancrecarb MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CFA (%)	[REDACTED] (b) (4)		
PP Population (n=18) CFA (%)	[REDACTED]		

Source: Adapted from Statistical Reviewer's Table (the results concur with those from the sponsor)

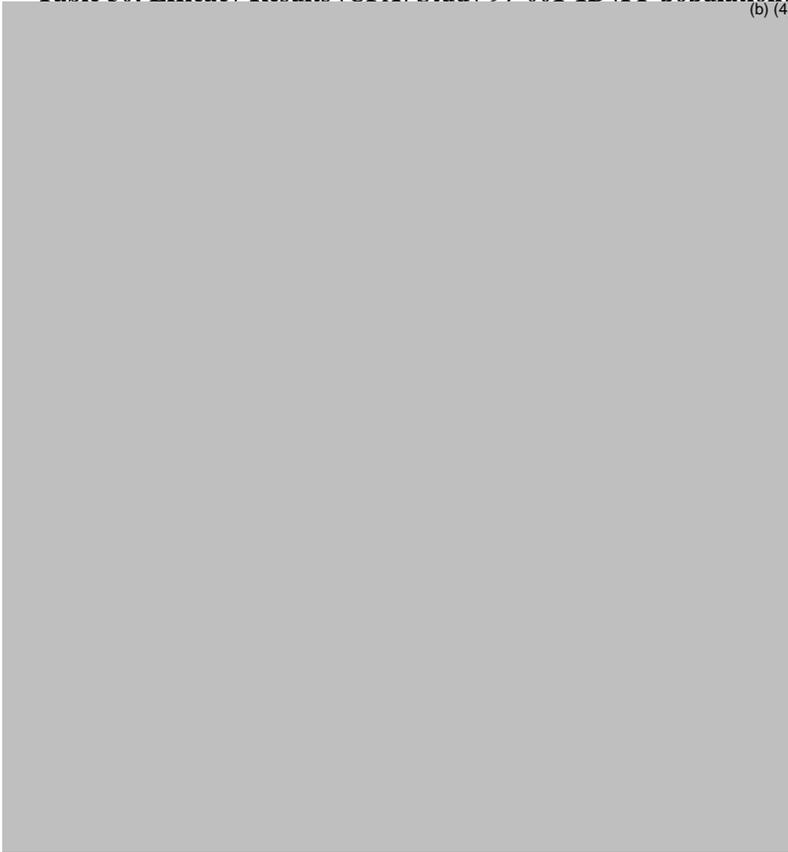
This reviewer performed an analysis of each individual's response to change in treatment (from Pancrecarb to placebo or vice versa). These results are shown below in Table 29, which represents the ITT population and Table 30, which represents the PP population. When analyzing the individual patient results, [REDACTED] (b) (4)

Clinically, an individual patient may have improved symptoms of malabsorption (diarrhea, abdominal pain, flatulence) with increasing CFA values.

Table 29: Efficacy Results (CFA) Study 97-001-1B (ITT population)
(b) (4)



Table 30: Efficacy Results (CFA) Study 97-001-1B (PP population)
(b) (4)



The outcomes for the two populations were vastly different; statistical significance could be shown in the PP population but not the ITT population.

According to the statistical reviewer, this study lacked clinical trial rigidity; it was open-label, there was no washout period between two crossover treatment periods, there were repeated treatment assessments, there was a change of analysis plan, etc. Therefore, the efficacy results were not reliable to support any efficacy claims.

In addition, in each individual patient, the changes in CFA were not clinically meaningful. It is difficult to determine the clinical significance of CFA values that differ by (b) (4). In conclusion, Study 97-001-1B was not sufficient to show the efficacy of Pancrecarb MS-8.

6.1.5 Analysis of Secondary Endpoint(s)

There were several secondary efficacy endpoints Study 06-001. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; (b) (4). The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Coefficient of Nitrogen Absorption (CNA)

A major secondary endpoint was the comparison of CNA after administration of Pancrecarb versus placebo.

The results showed that the mean CNA for Pancrecarb and placebo were 79% and 47%, respectively. The mean change in CNA was 32%, and this was a statistically significant change. (See Table 31 electronically scanned and copied from Sponsor.) These results were confirmed by the FDA Statistical Reviewer.

Table 31: Comparison of Percent Coefficient of Nitrogen Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	78.986	47.169	31.817 ^a	26.102, 37.533
Children (n = 10)	78.440	43.810	34.630 ^a	26.365, 42.895
Adults (n = 11)	79.532	50.528	29.005 ^a	21.183, 36.826

^a P<0.001

Source: 06-001 Study Report (Page 49, Section 11.1.1.2.1, Table11-3)

These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

Stool Frequency

A secondary endpoint was the comparison of stool frequency (number of bowel movements) between Pancrecarb and placebo recorded over the 72-hour stool collection period; The overall results showed stool frequency was 6.1 bowel movements/72 hours for Pancrecarb versus 10.1 for placebo treatment. The difference of 4, a 39.6% decrease in stool frequency with Pancrecarb compared to placebo treatment was statistically significant (P<0.001). (See Table 32 electronically scanned and copied from Sponsor)

Table 32: Comparison of Stool Frequency (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	6.086	10.089	-4.004 ^a	-5.607, -2.400
Children (n = 10)	5.591	9.409	-3.817 ^b	-6.136, -1.499
Adults (n = 11)	6.580	10.770	-4.190 ^a	-6.384, -1.995

^aP <0.001, ^b P=0.003

Source: 06-001 Study Report (Page 50, Section 11.1.1.2.2, Table11-5)

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Although statistically significant, the clinical significance of a four bowel movement difference over a 72 hour period is not clear.

Stool Weight

Another secondary endpoint was the comparison of stool weight between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool weight was 655.9 g/72 hours for Pancrecarb versus 1308.5 for placebo treatment. The difference of a 652.6 gram decrease in stool weight with Pancrecarb compared to placebo treatment, was statistically significant ($P < 0.001$). (See Table 33 electronically scanned and copied from Sponsor)

Table 33: Comparison of Stool Weight (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB [®] MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB [®] MS-16	Placebo		
Overall (n = 21)	655.939	1308.524	-652.585*	-813.369, -491.801
Children (n = 10)	507.129	1086.246	-579.117*	-811.610, -346.624
Adults (n = 11)	804.748	1530.802	-726.053*	-946.082, -506.024

* $P < 0.001$

Source: 06-001 Study Report (Page 51, Section 11.1.1.2.3, Table11-7)

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Once again, the clinical significance of a 653 gram difference in stool weight over a 72 hour period is not clear.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. Most secondary endpoints were subjective and assessed without using validated endpoint measures. Study 06-001 was of short duration and had a disproportionate amount of Pancrecarb treatment time, which made the analysis of treatment differences more difficult.

[Redacted] (b) (4)

For study 97-001-1B, the secondary efficacy endpoint was the comparison of CNA after administration of Pancrecarb MS-8 versus usual enzyme treatment.

In the ITT population, the results showed [Redacted] (b) (4)

In addition, since the clinical significance of CNA is not established, these secondary efficacy results are not clinically meaningful. (See Table 34 electronically scanned and adapted from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 34: Secondary Efficacy Results

	Pancrecarb MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CNA (%)			(b) (4)
PP Population (n=18) CNA (%)			

6.1.6 Other Endpoints

There are no other endpoints evaluated that are of clinical relevance.

6.1.7 Subpopulations

Subgroup analyses by age, and gender were performed by this Reviewer, and were found not to have affected the efficacy results in Study 06-001. There were too few non-Caucasian patients to perform a meaningful analysis by race. Since CF patients are mostly Caucasian, the homogeneity of race in the clinical development plan was felt to be representative of the larger CF population.

Analysis of patients by placebo (no treatment) CFA subgroups showed that the patients who were the most severely affected (lowest baseline CFA) gained the most benefit of Pancrecarb MS-16 treatment by having the largest increase in CFA (see section 6.1.4 Analysis of Primary Endpoint above).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients (except one) in the Pancrecarb clinical development program were treated according to CFF guidelines, and dosing did not exceed 2,500 U lipase/kg/meal and 10,000 U lipase/kg/day. The dose of Pancrecarb was determined on an individual basis, and patients' doses were titrated to control their symptoms of EPI while remaining within CFF guidelines.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects was not assessed in the Pancrecarb clinical development program since the clinical data obtained were from short-term studies. According to the literature, there does not appear to be the development of tolerance to PEPs and patients remain on these medications for long periods of time (typically life-long treatment).

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Study 97-001-2

This clinical study was a nonrandomized, open label, active controlled one-way cross-over study of ~50% decreased dose of Pancrecarb MS-8 in six CF patients ages 4-17. The primary endpoint was the change in CFA between usual PEP dose of Creon 10 or Creon 20 (Phase 1) and the ~50% reduced lipase dose of Pancrecarb (Phase 2). The results showed (b) (4)

The individual efficacy results are displayed below in Table 35.

Table 35: Study 97-001-2 Individual Results

Patient Number	CFA Phase 1 Creon 10	CFA Phase 1 Creon 20	CFA Phase 2 Pancrecarb	Phase 2 - Phase 1
001003				(b) (4)
001006				
001007				
001011				
001015				
001017				
Mean				

6.1.10.2 Study 2001-180

This clinical study was a nonrandomized, open label, active controlled one-way cross-over study of 50% decreased dose of Pancrecarb MS-4 in six CF patients ages 5-15. Pancrecarb MS-4 was administered to patients via gastrostomy tube (G-tube). The primary endpoint was the change in CFA between usual PEP dose (Phase 1) and 50% decreased dose of Pancrecarb MS-4 (Phase 2) directly into the G-tube. (b) (4)

Table 36: Study 2001-180 Individual Results

Patient Number	Phase	CFA
001001	1	(b) (4)
	2	
001003	1	
	2	
001004	1	
	2	
001005	1	
	2	
001006	1	
	2	
001007	1	
	2	

6.1.10.3 Study 092100

This clinical study was a randomized, double blind, placebo controlled, two-way cross-over study in of Pancrecarb MS-8 in Reducing Diarrhea Associated With Highly Active Antiretroviral Therapy (HAART) in HIV-Positive Patients. The primary efficacy variable was the reduction in frequency of diarrhea. The primary endpoint was comparison of number of formed stools between treatment periods (Pancrecarb MS-8 vs. placebo). (b) (4)

[Redacted text block]

No further analyses were performed on this study.

There were no other relevant efficacy analyses performed.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Safety data were reviewed from the nine clinical studies performed in the Pancrecarb clinical development program, including the two controlled studies 06-001 and 97-001B. Study 06-001 and 97-001B have been described in detail above in Section 5.3. The remaining studies included a number of different study designs (e.g., randomized, active-controlled, placebo-controlled, crossover, blinded, open-label and long-term follow-up). Study 092206 was an open-label placebo-controlled, single-treatment bioavailability study to determine the intestinal bioavailability of Pancrecarb in chronic pancreatitis (CP) patients with EPI. Safety was assessed in these studies by the review of all of the AE data.

The most important study reviewed for safety was 06-001, which was the double blind, placebo-controlled study in CF patients; however, all of the safety data from the Pancrecarb clinical studies were reviewed in its entirety.

7.1.2 Adequacy of Data

In the opinion of this Reviewer, the Sponsor adequately categorized the adverse events using MedDRA classification.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

There was general pooling of safety data for this review. Although, the study designs were different, most of the studies had a similar patient population (CF patients) and many had a similar primary endpoint (change in CFA). In addition, for the two controlled studies, each study was analyzed separately (see Section 5 above).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety of Pancrecarb was evaluated in nine clinical studies. In eight individual studies, subjects were treated for one to four weeks duration with Pancrecarb. In one study, patients receiving Pancrecarb were followed for up to 2 years. The safety population was defined as any subject who received at least one dose of Pancrecarb. Thus, the safety population includes 262

subjects exposed to Pancrecarb covering a treatment period of seven days to more than two years.

According to the PEP Guidance, it was acceptable that the Pancrecarb clinical program was limited to short-term efficacy and safety studies with the one exception of Study 091897, which was a long-term, non-randomized, uncontrolled, open-label study. The long-term safety of PEPs has been established over the many years of their use. This application relied on the published medical literature for full descriptions of AE profiles.

The overall exposure to Pancrecarb was as follows in Table 37 (electronically copied and reproduced from the Sponsor's submission).

Table 37: Mean Lipase Doses and Duration of Dosing in Clinical Studies

Study No.	Duration of PANCRECARB® Treatment	Lipase Dose Measure	PANCRECARB® Mean Lipase Units		Comparator Mean Lipase Units
06-001			PANCRECARB® MS-16		Placebo
	7 days	Units/kg/meal	1,565 (SD 563)		n/a
97-001-1B			PANCRECARB® MS-8		Usual Enzyme*
	7 days	Units/kg/meal	1,158 (SD 429)		1,145 (SD 448)
		Units/kg/day	4,237 (SD 1,873) ^a		4,189 (SD 1,913)
091897			PANCRECARB® MS-8		Initial History
	Up to 2 years	Units/kg/day	4,576 (SD 3,071)		9,898 (SD 12,004)
97-001-2			PANCRECARB® MS-8		Creon® 10 or 20
	7 days	Units/kg/day	8,682 (SD 3,369)		16,519 (SD 7,207)
071503			PANCRECARB® MS-16		Usual Enzyme*
	14 days	Units/kg/day	5,430 (SE 510)		7,838 (SE 637)
2001-180			PANCRECARB® MS-4		Viokase® powder ^b
	30 days	Units/kg/day	4,490 (SE 1,251)		9,128 (SE 1,251)
020296			PANCRECARB® MS-8 ^c		Cotazym® ECS-8
	14 days	Units/kg/day	6,071 (SD 1,072)		6,810 (SD 1,860)
111395			PANCRECARB® MS-8 ^c		Usual Enzyme**
	14 days (per phase)	Units/day	Phase 2 273,143 (SD 153,014)	Phase 3 192,503 (SD 87,907)	Phase 1 323,200 (SD 153,823)
		Units/kg/day ^d	5,811	4,096	6,875
092100			PANCRECARB® MS-8		Placebo
	7 days	Capsules/Day	6.9 (SD 2.8)		n/a

*Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcan/Scandipharm)

**Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-16 (Ortho/McNeil); Ultrase® MT-20 (Axcan/Scandipharm); Cotazym® ECS-8 (Organon)

^a Units/kg/day represent an approximate 48% reduction from the patients' usual lipase dose of 8,760 units, calculated from the average of the range of the number of capsules per day at study entry.

^b Viokase® is a registered trademark of Axcan/Scandipharm.

^c A previous formulation of PANCRECARB® (pancrelipase) MS-8 drug product was used in these studies.

^d Units/kg/day estimated using a mean body weight of 47kg.

n/a = not applicable

The data in the Pancrecarb clinical development program were limited by several factors which included: small study size, use of only one pivotal study, a homogeneous study population, and short study duration. However, given the extensive knowledge of PEPs worldwide, the overall Pancrecarb safety program was adequate for the MS-16 dosage strength, and was consistent with the recommendations of the Guidance.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients were titrated to relief of symptoms, and remained within CFF guidelines (except one patient). All of the dosage strength tablets were used in the clinical development program; however, only the MS-16 dosage strength had its efficacy demonstrated.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the Pancrecarb clinical development program. In addition, this was a 505(b)(2) application, thus no special animal or in vitro testing was required.

7.2.4 Routine Clinical Testing

The schedule of clinical assessments performed for the pivotal study, 06-001, was adequate (see schedules of study visits for Study 06-001 in Section 5.3), and consisted predominantly of monitoring for AEs during study drug treatment, and changes from baseline in physical examinations (including vital signs) and clinical laboratory assessments (chemistry, hematology and urinalysis). The efforts to elicit AEs were acceptable. Since PEPs are not absorbed, no ECGs were collected.

Clinical laboratory evaluations were conducted in only three studies: 06-001, 111395 and 2001-180. Vital signs and physical examination information were collected while on treatment with Pancrecarb only in Studies 06-001, 111395, and 071503.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pancrecarb acts locally in the GI tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed and absorption, distribution, metabolism, and elimination (ADME) assessments were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There is an extensive history of clinical use with the PEPs, and their safety profile is well described. The most serious safety concern with PEP administration is fibrosing colonopathy (FC). FC is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs. As a result of this potential safety (and efficacy) concern, the CFF and FDA published weight-based dosing guidelines for PEP administration (see Section 2.1).

The clinical development program for Pancrecarb followed the current CFF recommendations on limiting the dosages (by lipase units). No cases of fibrosing colonopathy were reported in the

clinical development program; however, it is noted that cases of FC are rare, and the finding of even a single case of FC in a safety population of this size was not expected.

PEP treatment has been associated with elevated serum and urine levels of uric acid (hyperuricemia and hyperuricosuria). Uric acid levels were adequately monitored throughout the pivotal clinical study. No clinically significant uric acid elevations were reported; however, given the short duration of treatment and the treatment of patients who were of adequate nutritional status only, most of whom were maintained on stable doses of PEPs prior to entry into these studies, clinically meaningful changes in uric acid levels were not expected.

Despite the negative findings for FC, hyperuricemia, and hyperuricosuria in the short-term clinical development program for Pancrecarb in a small number of patients, given the concerns for these AEs with the administration of PEPs, caution should be exercised when prescribing PEPs to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels. In addition, monitoring for FC should be addressed in any future labeling for Pancrecarb, and should be a component of ongoing safety monitoring/pharmacovigilance of Pancrecarb.

7.3 Major Safety Results

7.3.1 Deaths

Four deaths were recorded during the 2-year long term (091897) study period; none were attributed to the use of Pancrecarb MS-8. No other deaths were reported during any other study with Pancrecarb. The deaths are summarized below in Table 38 (electronically copied and reproduced from the Sponsor's submission).

Table 38: Summary of Deaths Recorded during Study 091897

Subject	Demographics	Cause of Death	Date Enrolled	Date of Death (b) (4)
01A-001	Male, Age 10	Sepsis, neurological insult	8/1998	
12A-04A	Female, Age 44	Evac pseudo pneum/malnutrition, end stage disease	10/21/1998	
17A-009	Male, Age 27	Acute rejection of double lung transplant	8/1/1999	
18A-003	Female, Age 30	Pulmonary disease	1/24/2000	Unknown

Reference: [Study 091897 CSR Table 8](#)

7.3.2 Nonfatal Serious Adverse Events

Overall in the Pancrecarb clinical development program, three Pancrecarb treated patients experienced four AEs that were considered serious by the study investigator(s). None of the SAEs were considered related to treatment. Following are summary narratives of the individual SAEs.

Study 071503: During the Phase 2 (Pancrecarb MS-16) treatment period, one patient (Site 2: #111) was hospitalized with 2 SAEs, “CF exacerbation” and “sinusitis” which were categorized as mild in intensity and not related to study medication. These events were actually first reported as symptoms in Phase 1. The events completely resolved during the study observation period

Study 2001-180: During the Phase 2 (Pancrecarb MS-4) treatment period, one patient (001004) reported being involved in a motor vehicle accident (MVA) and was hospitalized, resulting in their discontinuation from the study. The event was categorized as moderate intensity, definitely not related to study drug, and resolved completely.

Study 06-001: At the follow-up visit (Day 14) at the end of Treatment Period 2, a 10 year old female patient (184-002) experienced an SAE of CF. The patient received Pancrecarb MS-16 during Treatment Period 2. The SAE was assessed as mild and judged not related to the study drug by the Investigator. The SAE was treated with concomitant medication, although no new concomitant medication was prescribed. The SAE was assessed as resolved at an unscheduled visit to follow the SAE.

7.3.3 Dropouts and/or Discontinuations

Overall, 22 patients (8%) from the total safety population of 262 discontinued for reasons attributed to AE(s), 18 of those 22 were receiving Pancrecarb. Table 39 below summarizes the details for individual patients who discontinued due to AE(s). The majority of the AE(s) were gastrointestinal in nature. The long-term study (091897) contributed 13 of the 18 Pancrecarb patients who discontinued due to AE(s). These discontinuations were reported on the CRF AE page and were included in the ISS AE database. The Sponsor reports that an additional seven patients discontinued Study 091897 for reasons noted to be due to AE(s) on the CRF clinical summary page. However, due to insufficient information, these events were not included in the ISS AE database.

This reviewer examined the reports for each of the additional seven patients who were discontinued from the study 091897 due to an adverse event. Every discontinuation was secondary to an AE which was gastrointestinal in nature.

Table 39: Discontinuations Attributed to AEs

Study Number	Treatment Group	Patient number	Adverse Event	Intensity
06-001	Placebo	007-006	Decreased weight	Moderate
06-001	Placebo	009-005	Hyperglycemia and elevated LFTs	Moderate Moderate
111395	Usual lipase	005	Stomach ache	Moderate
97-001	Usual lipase	001006	Pulmonary exacerbation and Fever	Severe Severe
071503	Pancrecarb	001	Nausea and Abdominal cramps	Moderate Moderate
97-001-2	Pancrecarb	001007	Fever	Severe
111395	Pancrecarb	008	Abdominal pain	Moderate
111395	Pancrecarb	009	Stomach cramping	Moderate
020296	Pancrecarb	017	Abdominal discomfort	Moderate
091897	Pancrecarb	10A110	Blood in stool	Mild
091897	Pancrecarb	10A111	Abdominal pain and Malabsorption	Severe Moderate
091897	Pancrecarb	10A112	Cramps and malabsorption	Severe Severe
091897	Pancrecarb	12A001	Abdominal cramp and diarrhea	Severe Severe
091897	Pancrecarb	12A010	Abdominal cramps and diarrhea	Severe Severe
091897	Pancrecarb	13A003	Increased bloating and gas	Moderate Moderate
091897	Pancrecarb	13A006	Increased number of stools and gas	Moderate Moderate
091897	Pancrecarb	13A008	Fat in stools and increased of stools	Moderate Moderate
091897	Pancrecarb	13A011	Increased BM's, gas, pain	Unknown
091897	Pancrecarb	13A020	Increased number of stools	Moderate
091897	Pancrecarb	13A024	Increased abdominal pain and gas	Moderate Moderate
091897	Pancrecarb	13A026	Increased bloating gas and pain	Unknown
091897	Pancrecarb	16A009	Increased gas	Moderate

7.3.4 Significant Adverse Events

The long term study (091897) was comprised of CF patients that were on Pancrecarb MS-8 therapy for up to 2 years. In this study, hospitalization alone was not considered a SAE. Based on the study design and documentation instructions, if hospitalization was related to Pancrecarb the “Adverse Experience Report” form was to be completed. Overall, 45 subjects enrolled in the long term study (091897) were hospitalized at some time during the 2-year study period. Hospitalizations were mostly due to CF disease related events. None of the hospitalizations were considered by the study site investigators or this Reviewer to be related to the use of pancreatic enzymes.

During Study 111395, two patients (004 and 007) were hospitalized due to exacerbation of their underlying CF. These hospitalizations were not reported as SAEs per the protocol. Both patients completed the study and the events were not considered related to enzyme treatment.

Two cases of hypersensitivity reactions were reported:

- In Study 97-001B, a 17-year-old male (patient #005), experienced a moderate intensity rash during Phase 2 (Pancrecarb MS-8) which was considered possibly related to study medication. No action was taken and the event resolved completely.
- In Study 06-001, a 17-year-old female (patient 007-009), experienced a mild rash during Phase 2 (Pancrecarb MS-16) which was considered unrelated to study medication, and which resolved with concomitant medication.

7.3.5 Submission Specific Primary Safety Concerns

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). See section 7.2.6 (above).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Since the Pancrecarb development program consisted of nine clinical studies, many of which had different study designs, AEs in patients treated with Pancrecarb were analyzed separately from those AEs in patients taking their usual PEP (active control) and patients taking placebo. The assessment of AEs for causality and severity were made by the clinical investigator(s) responsible for each respective study.

Pancrecarb

Of the 262 patients treated with Pancrecarb that were enrolled in a total of 9 clinical studies, 77 (29%) experienced 148 adverse events. Of these, 36 (14%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. The most commonly reported AE (>5% incidence) in the Pancrecarb treated safety group was abdominal pain, with 14 events reported, 11 of which were considered related to treatment. There were 7 reports of severe abdominal pain, 6 of which were considered related to treatment. Other AEs reported for patients treated with Pancrecarb included abdominal pain upper and headache (n=8 each), diarrhea and flatulence (n=7 each), abdominal distension and frequent bowel movements (n=6 each). Three patients experienced four AEs that were considered serious by the study investigator(s). None of the SAEs were considered related to Pancrecarb treatment [see Section 7.3.2.].

Usual Lipase

There were six active-controlled studies included in the Pancrecarb NDA. The following brands of PEPs were included in these studies: Creon® 10 and 20 (Solvay Pharmaceutical); Pancrease® MT-10, MT-16 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcan/Scandipharm); Cotazym® ECS-8 (Organon), and Viokase® powder (Axcan/Scandipharm).

Of the 87 patients treated with their usual lipase, 20 (23%) experienced 26 adverse events. Of these, 7 (8%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. There were no SAEs reported.

The most commonly reported AE (>2% incidence) in the usual lipase treatment group was headache, with six events reported which were considered related to treatment. There were two reports of moderate abdominal pain which were considered related to treatment. There were two reports of severe pyrexia which were not considered related to treatment.

Placebo

There were two placebo-controlled studies included in the Pancrecarb NDA. Of the 37 placebo treated patients, 18 (49%) experienced 65 adverse events. Of these, 15 (40%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. There were no SAEs. The most commonly reported AEs (>5% incidence) in the placebo treatment group were abdominal pain/distension, flatulence, headache, and decreased weight, the majority of which were considered related to treatment. There were two reports each of nasal congestion and pharyngolaryngeal pain which were not considered related to treatment.

For a detailed review of adverse events for Study 06-001 and Study 97-001-1B see Sections 5.3.1.11.7.2 and 5.3.2.11.3.2.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were conducted in only three studies: 06-001, 111395 and 2001-180. In Study 06-001, there were two patients who had laboratory results that were considered by the investigator to be clinically significant. One patient (009-005) had hyperglycemia and elevated liver function tests while on placebo during Treatment Period 1. One patient (007-008) on Pancrecarb had an abnormal urinalysis (which showed large hemoglobin) at the end of Treatment Period 2. However, both these abnormalities were present at Screening and slightly improved at the End of Study Visit and Follow-up visits.

This review identified an additional patient (191-003) in Study 06-001 who had an elevated alkaline phosphatase level after Treatment Period 1 (580 U/L) and a markedly elevated alkaline phosphatase level at the Follow-up visit (1445). Of note, is that this patient had a history of “active CF liver disease” and baseline elevated blood levels of AST, ALT and GGT.

This reviewer reviewed these individual cases and concluded that these isolated cases could not confer clinical meaningfulness. No clinical consequences were noted from any of the above findings.

Study 111395 was a ten patient non-randomized, open-label, active-controlled, one-way crossover study wherein an older formulation ^{(b) (4)} of Pancrecarb was used. Clinical laboratory testing was performed at baseline and after completion of each of the two Pancrecarb dosing phases. This reviewer reviewed the laboratory values for each patient; there were no clinically relevant changes in laboratory values.

Study 2001-180 was a seven patient non-randomized, open-label, active-controlled, one-way crossover study wherein the MS-4 dosage formulation was administered into a gastrostomy tube. This reviewer reviewed the laboratory values for each patient; there were no clinically relevant changes in laboratory values.

7.4.3 Vital Signs

Vital signs and physical examination information were collected while on treatment with Pancrecarb only in studies 06-001, 111395, and 071503. In these studies, no clinically relevant changes were observed.

7.4.4 Electrocardiograms (ECGs)

Pancrecarb is not systemically absorbed and electrocardiogram evaluation was not part of the Pancrecarb clinical development program.

7.4.5 Special Safety Studies

There were no special safety studies performed in the Pancrecarb clinical development program.

7.4.6 Immunogenicity

Pancrecarb and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the Pancrecarb clinical development program.

7.5 Other Safety Explorations

No other safety explorations were performed. No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Pancrecarb and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the PEP clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

No studies with Pancrecarb were conducted in pregnant women. It is likely that Pancrecarb will be used by pregnant women and women of reproductive potential. PEPs have likely been used over their history by pregnant women, but are not absorbed and no known effects of active

ingredients on pregnant women or their offspring are known. The labeling of this product should address safety in pregnancy.

7.6.3 Pediatrics and Effect on Growth

PEPs are widely recognized as having a positive effect on growth in pediatric patients with CF.^{4,5} Studies performed in the Pancrecarb clinical development program were, for the most part, short-term studies where long-term growth and development were not assessed, which is consistent with the recommendations for study designs in the Guidance for submitting PEP NDAs. One long-term (up to two years) study, 091897, which was performed as part of the Pancrecarb clinical development program, had weight gain as the primary endpoint. However, the non-randomized, uncontrolled, open-label study design did not allow for reliable interpretation of the data. Thus, no accurate formal assessments of pediatric growth and development were performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

PEPs are not systemically absorbed and there is no potential for abuse, withdrawal, or rebound.

An important safety issue regarding PEP use and the potential for overdose is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.^{4,5} In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children <4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.

⁴ Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatrics*.127(5), Nov 1995, pp 681-684. (PMID: 7472816)

⁵ Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. *Best Pract Res Clin Gastroenterol*. 2006; 20(3):531-46. (PMID: 16782527)

- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Recommendations for snacks are half the dose taken at meals. Daily doses are not to exceed 10,000 U lipase/kg/day (3 meals, 2 snacks).

These recommendations should be included in product labeling for Pancrecarb and for all PEPs.

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted by the Sponsor on March 17, 2009. Pertinent findings from the report are presented below:

The Sponsor reports that all Pancrecarb studies were completed with the safety information included in the original NDA, with the exception of Study Protocol 092206 entitled *Bioavailability of Pancreatic Enzymes in the Human Upper Intestine (duodenum) from Pancrecarb Delayed Release Capsules, Buffered and Enteric-Coated Microspheres*. Three additional patients have been enrolled at St. Louis University and completed the study with no adverse events reported. Four additional patients have been enrolled at another study site, University of North Carolina: Two patients discontinued the study during Phase 1 (placebo) due to procedurally related emesis, and two patients completed the study with no AEs reported.

Thus, there were no new or additional safety findings reported in the 120-day Safety Update.

8 Postmarketing Experience

Pancrecarb capsules were introduced onto the US market by Digestive Care, Inc. in 1995 as a physician prescribed pancreatic enzyme replacement therapy. Annual Drug Product Reviews have been prepared since 2002. Over this period of time, only two product complaints relating to an adverse drug reaction have been reported. A case of Distal Intestinal Obstructive Syndrome (DIOS) was reported that was determined to be congenital and not considered by the physician to be related to treatment with Pancrecarb, and one case of allergic reaction (itching and red, blotchy rash on face) in a patient with a history of allergy to another pancrelipase product.

The manufacturer does not have specific data on the number of patients treated with Pancrecarb. However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b) (4) Pancrecarb capsules were shipped to wholesalers. If the usual range of daily intake of Pancrecarb is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pancrecarb on an annual basis.

9 Appendices

9.1 Literature Review/References

Please see individual references noted throughout this review.

9.2 Labeling Recommendations

Since this NDA is recommended to receive a Complete Response action, the labeling was not negotiated with the Sponsor during this review cycle. However, should Pancrecarb be approved during a future review cycle recommendations for future labeling should include:

- Recommended indication: Pancrecarb is indicated for the treatment of steatorrhea due to EPI due to a variety of causes, including CF and CP.
- Viral issues: Since PEPs are derived from pig pancreata, there is a theoretical and potential risk of transferring certain species-specific viruses to patients taking PEPs (e.g., porcine parvovirus). Thus, labeling should note that live virus are present in the capsule, and that potential risk of transmission exists, although no human transmission due to PEP exposure has been reported to date.
- Dosage recommendations: To follow CFF recommendations; see Section 7.6.4 .
- Warnings: Cases of fibrosing colonopathy has been reported in young CF patients on high doses of PEPs. There have been reports of elevated serum and urine uric acid levels in patients taking PEPs.
- Dosing instructions: do not open microtabs to estimate doses.
- Secondary endpoints: not to be included in labeling.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22175	----- ORIG 1	----- DIGESTIVE CARE INC	----- PANCRECARB

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/s/

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08/27/2009

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