

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-175Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 17, 2012
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-175
Applicant	Digestive Care, Inc.
Date of Submission	November 18, 2011
PDUFA Goal Date	May 18, 2012
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"> ▪ Pertzye 8,000 lipase/28,750 protease/30,250 amylase ▪ Pertzye 16,000 lipase/57,500 protease/60,500 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Approval under 21 CFR 314

Table of Contents

1. Introduction.....	3
2. Background.....	4
3. CMC.....	9
4. Nonclinical Pharmacology/Toxicology	23
5. Clinical Pharmacology/Biopharmaceutics.....	24
6. Clinical Microbiology.....	29
7. Clinical/Statistical - Efficacy	30
8. Safety	36
9. Advisory Committee Meeting.....	41
10. Pediatrics.....	42
11. Other Relevant Regulatory Issues.....	44
12. Labeling	45
13. Recommendations/Risk Benefit Assessment.....	47
APPENDIX 1: CFF Dosing Guidelines.....	53
APPENDIX 2: List of Pertzye Clinical Studies.....	55
APPENDIX 3: DAIOP Consult Memo	56
APPENDIX 4: NDA Deficiency Items – First Action	58
APPENDIX 5: DS Deficiency Items – August 28, 2009.....	62
APPENDIX 6: DS Microbiology Deficiency Items – May 3, 2010.....	65
APPENDIX 7: Summary of Observations Cited in FDA Form 483 (issued to DCI, to (b) (4) and to (b) (4)).....	66
APPENDIX 8: Summary of HHE Review – February 23, 2010.....	69
APPENDIX 9: NDA Deficiency Items – Second Action.....	70
APPENDIX 10: DS Deficiency Items – October 27, 2010	74
APPENDIX 11: Biopharmaceutics Additional Comments – Second Action.....	76

1. Introduction

A Complete Response (CR) Letter was sent by the Division on January 27, 2011. This resubmission, received November 18, 2011, is a complete response to that letter, and represents the third 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 both the first and second review cycles, deficiencies were identified by the Chemistry, Manufacturing, and Controls (CMC) discipline. In addition, there was one Clinical Pharmacology deficiency item in each of the CR letters, one Clinical deficiency item in the first CR letter, and one Facility Inspection deficiency item in the second CR letter.

CMC deficiencies in the first review cycle (Items #1 to #18 of the first CR letter) 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 (u) (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).

CMC deficiencies in the second review cycle (Items #1 to #7 in the second CR letter) were related to: (1) deficiencies in drug substance (separate letter with (b) (4) deficiency items sent to the drug substance DMF holder on October 27, 2010, and additional information requested in a meeting on November 15, 2010); (2) request for prospective process validation reports; (3) release and stability acceptance criteria; (4) real-time stability data to support the requested expiry dating; (5) reference standard qualification program; (6) request for accelerated and/or stressed stability studies in annual stability program; and (7) RP-HPLC assay used in release and stability testing.

The Clinical Pharmacology deficiency item in the first review cycle (Item #19 in the first CR letter) 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 Pharmacology deficiency item in the second review cycle (Item #8 in the second CR letter) stated that validation reports submitted in response to the above (Item #19 in the first CR letter) were not complete, and recommended an evaluation of in-process assay performance; it also recommended a comprehensive applesauce compatibility report.

The Clinical deficiency item in the first review cycle (Item #20 in the first CR letter) 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)

In the second review cycle, in response to the Clinical deficiency item in the CR Letter (Item #20 in the first CR letter), the Applicant (b) (4)

(b) (4) provided process validation, release and stability data, and dissolution data for the new (b) (4) MS-8 capsules.

It should be noted that in the current submission, the Applicant is pursuing approval of (b) (4) the MS-8 and MS-16 capsule strengths (b) (4)

The facility inspection deficiency item in the second review cycle (Item #9 in the second CR letter) stated that the drug substance DMF Holder's response to the FDA form 483 deficiencies was not adequate.

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: Six 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
- (5) Ultresa (NDA 22-222): approved March 1, 2012
- (6) Viokace (NDA 22-542): approved March 1, 2012

Thus, there are five approved PEPs (Creon, Zenpep, Pancreaze, Ultresa, and Viokace) 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; 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.

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.

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: 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).

It should be noted that a Risk Evaluation and Mitigation System (REMS) was implemented at the time of approval of the first three approved PEPs (Creon, Zenpep, and Pancreaze) in order to ensure that the benefits of the drug outweighed: (1) the known risk of fibrosing colonopathy which may be mitigated by properly dosing each of the PEPs; and (2) the theoretical risk of transmission of viral disease to patients treated with a porcine-derived pancreatic enzyme product. However, after consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), the Division determined that a REMS is no longer necessary to ensure the benefits of the drug outweigh the risks described above because labeling is adequate to describe the risks. The Medication Guide will continue to be part of the approved labeling. Letters indicating that the REMS was no longer required were sent to the sponsors of these three approved PEPs – Creon (May 9, 2011), Zenpep (June 10, 2011), and Pancreaze (June 20, 2011). A REMS was not implemented for the PEPs approved on March 1, 2012 (Ultresa and Viokace).

2.2.2 Regulatory History of Pertzye

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

Table 2. Pertinent Regulatory History of Pertzye

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 Action (1 st action)
July 2010	Class 2 Resubmission of NDA 22-175
January 2011	Complete Response Action (2nd action)
June 2011	Meeting with the Division to discuss CMC, Clinical Pharmacology, and facility inspection deficiencies in the Complete Response Letter
November 2011	Class 2 Resubmission of NDA 22-175 (current submission)

* 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.” The pivotal study (06-001) used the MS-16 formulation.

In the current submission, the applicant is pursuing approval for (b) (4) the MS-16 and MS-8 formulations (b) (4). Note that the previously marketed “MS-16” and the “MS-16” proposed in this submission are the same formulation; however, the previously marketed “MS-8” formulation differs from the “MS-8” formulation proposed in this submission. (b) (4)

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

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

- Cross Discipline Team Leader Review by Anil Rajpal, dated August 27, 2009
- Cross Discipline Team Leader Review by Anil Rajpal, dated January 27, 2011
- 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 November 18, 2011. It was classified as a six-month resubmission with a PDUFA deadline of May 18, 2012.

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 Review of Safety Update by Marjorie Dannis, dated December 23, 2011 (NDA 22-175)
- (2) CMC Reviews from the Division of Therapeutic Proteins (DTP):
 - (a) NDA Review by Howard Anderson dated April 17, 2012 (NDA 22-175)
 - (b) CMC Summary Review by Emanuela Lacana dated May 16, 2012 (NDA 22-175)
 - (c) DMF Review by Richard Ledwidge dated May 15, 2012 (DMF (b) (4))
 - (d) DMF Review by Richard Ledwidge dated February 1, 2012 (DMF (b) (4))
- (3) ONDQA Biopharmaceutics Review by Tien-Mien Chen dated April 22, 2012 (NDA 22-175)
- (4) Clinical Pharmacology Review by Dionna Green dated April 20, 2012 (NDA 22-175)
- (5) Microbiology Reviews from New Drug Microbiology Staff (NDMS):
 - (a) NDA Review by Vinayak Pawar dated February 3, 2012 (NDA 22-175)
 - (b) DMF Review by Stephen Langille dated January 31, 2012 (DMF (b) (4))
- (6) Pediatric and Maternal Health Staff (PMHS) Review by Elizabeth Durmowicz dated March 6, 2012 (NDA 22-175)
- (7) Division of Medication Error Prevention and Analysis (DMEPA) Reviews:
 - (a) Proprietary Name Review by Manizheh Siahpoushan dated February 10, 2012 (NDA 22-175)
 - (b) Label and Labeling Review by Manizheh Siahpoushan dated February 23, 2012 (NDA 22-175)
- (8) Office of Prescription Drug Promotion (OPDP) Review by Twyla Thompson dated April 12, 2012 (NDA 22-175)
- (9) Study Endpoint and Labeling Development (SEALD) Review by Jeanne Delasko dated April 17, 2012 (NDA 22-175)
- (10) DTP Carton and Container Label Review by Kimberly Rains, dated April 17, 2012 (NDA 22-175)

Correspondence from the current review cycle that was cited by this reviewer consisted of the following:

- Proprietary Name Request Conditionally Acceptable Letter sent to Digestive Care, Inc. dated February 10, 2012 (signed by Carol Holquist, Director Division of Medication Error Prevention and Analysis [DMEPA])

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

3. CMC

The reader is referred to the CMC Primary Review by Howard Anderson dated April 17, 2012 (NDA 22-175) and the CMC Team Leader Summary Review by Emanuela Lacana dated May 16, 2012 (NDA 22-175) 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 were recently approved (March 1, 2012).

The drug substances used in each of the products are 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 first CR letter (see Appendix 4), the applicant developed new (b) (4) MS-8 capsules (b) (4) and 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 Section 3 CMC and Section 5 Clinical Pharmacology/Biopharmaceutics of this CDTL Review (see Sections 3.2 and 5.2). In the current submission, the Applicant is pursuing approval of (b) (4) the MS-8 and MS-16 capsule strengths (b) (4)

Packaging: The MS-8 and MS-16 capsules are packaged in white polyethylene bottles with 100 and 250 counts. 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 (b) (4) were related to (see final wording of Items #17 to #23 in the Deficiency Letter sent to (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 (b) (4) were related to (see final wording of Items #3 to #16 in the Deficiency Letter sent to (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).

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 Pertzye. 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 Second Review Cycle

In the second review cycle, a CMC Primary Review was conducted by Howard Anderson, and a CMC Team Leader Summary Review was conducted by Emanuela Lacana. (Please refer to the CDTL review, and each of the individual reviews for more information.)

3.2.1 DS Viral Issues (second cycle)

Many of the DS viral issues identified in the first review cycle of Pertzye were addressed in the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF. In the 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 Sections 3.3.1 and 13.6 of this CDTL review.)

3.2.2 DS Non-Viral Issues (second cycle)

Many of the DS non-viral issues identified in the first review cycle of Pertzye were addressed in the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF. In the 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 review cycle of that application was adequately addressed. However, the secondary CMC reviewer identified an additional deficiency item.

The deficiency item for DS non-viral issues that was sent to (b) (4) was related to (see final wording of Item #6 in Deficiency Letter sent to (b) (4) in Appendix 10): data demonstrating no adverse impact on product quality from a change in the DS intermediate storage container from (b) (4) to (b) (4) drums.

In addition, there were a number of microbiology issues (see Section 3.2.4 of this CDTL Review).

3.2.3 DP Issues (second cycle)

The overall findings of the DP reviewers in the second 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. (See CDTL Review from second review cycle).

Deficiency items for DP issues that were sent to DCI were related to (see final wording of Items #2 to #7 in the CR Letter in Appendix 9): (2) request for prospective process validation reports; (3) release and stability acceptance criteria; (4) real-time stability data to support the requested expiry dating; (5) reference standard qualification program; (6) request for accelerated and/or stressed stability studies in annual stability program; and (7) RP-HPLC assay used in release and stability testing.

3.2.4 Microbiology Issues (second cycle)

Many of the microbiology issues identified in the first review cycle of Pertzeye 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 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 Appendix 10) 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) (see Appendix 10) have been adequately addressed.

The deficiency items for microbiology issues that were sent to (b) (4) were related to (see final wording of Items #7 to #14 in Deficiency Letter sent to (b) (4) in Appendix 10): (7) efforts to reduce the bioburden on incoming pancreas glands; (8) microbial limits specification; (9) updated manufacturing procedures including timepoints for microbiological samples; (10) microbiological monitoring of (b) (4); (11) microbiological alert and action levels; (12) commitment to clean processing equipment between batches; (13) updated microbial limits acceptance criteria for stability batches of DS; and (14) release test procedure for *Bacillus cereus*, and commitment to test each batch of DS for *Bacillus cereus* prior to release.

3.2.5 Facility Inspections (second cycle)

Information from Establishment Evaluation System (EES) reports for each of the facility inspections (for DCI, (b) (4) and (b) (4)) is shown below:

- DCI: "Withhold" recommendation from the Office of Compliance for DCI dated January 25, 2011.
- (b) (4): "Withhold" recommendation from the Office of Compliance for (b) (4) dated November 18, 2010.
- (b) (4): "Withhold" recommendation from the Office of Compliance for (b) (4) (contract testing laboratory for (b) (4)) dated September 22, 2010.

A summary of each of the observations cited in the FDA Forms 483 issued to DCI, (b) (4), and (b) (4) (contract testing laboratory for (b) (4)) is provided in Appendix 7 of this CDTL Review. It should also 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 (see summary of the HHE Review in Appendix 8 of this CDTL Review).

The Office of Compliance issued (b) (4).

3.3 Current Review Cycle

3.3.1 DS Viral Issues (current cycle)

A separate DS Viral Issues Review was not conducted during the current (third) review cycle. The DS viral issues deficiencies identified in the second review cycle were deemed to not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's) (see Section 3.2.1 of this CDTL review).

DS Viral Postmarketing Commitments (PMC's):

DS viral items to be communicated to (b) (4) (taken from Dr. Anderson's review) as postmarketing commitments (PMC's) are provided below. (b) (4) provided the dates shown below on March 29, 2012, and DCI agreed with the dates on April 13, 2012. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

DS PMC #1: Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.

Final Report Submission by September 1, 2012

DS PMC #2: Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

Final Report Submission by March 1, 2013

DS PMC #3: Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

Final Report Submission by March 1, 2013

DS PMC #4: Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program should include the selection of

(b) (4)

human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

Final Report Submission by May 15, 2013

DS PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria should be submitted to the Agency.

Final Report Submission by April 15, 2013

DS PMC #6: Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

Final Report Submission by June 1, 2012

DS PMC #7: Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

Final Report Submission by March 15, 2013

3.3.2 DS Non-Viral Issues (current cycle)

The DS non-viral issues identified in the previous (second) review cycle of Pertzye were addressed during the reviews of other NDA's (i.e., Ultresa and Viokace NDA's) that used the same DS DMF. In the DS review (dated February 1, 2012; filed under DMF (b) (4)), the DS Reviewer (Richard Ledwidge) concluded that a deficiency exists, but does not preclude approval of the application since this can be addressed as a postmarketing commitment (PMC). In addition, the secondary CMC Reviewer identified another PMC for the Pertzye application (see Review by Emanuela Lacana dated May 16, 2012).

DS Non-Viral Postmarketing Commitments (PMC's):

DS non-viral items to be communicated to (b) (4) (taken from Dr. Lacana's review) as postmarketing commitments (PMC's) are provided below. (b) (4) provided the dates shown below on March 29, 2012, and DCI agreed with the dates on April 13, 2012. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

DS PMC #8: Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

Final Report Submission by June 1, 2012

DS PMC #9: Revise release specifications after 30 lots of drug substance 1206 and 1208 lots have been manufactured.

Final Report Submission by May 15, 2013

(b) (4) Response (to Deficiency Item #6):

A summary of the DS reviewer's assessment of the adequacy of (b) (4) response to each of the parts (a-d) of Item #6 in the letter to (b) (4) (see Appendix 10) is presented below:

- (6a) Extractable/leachable studies and risk analysis on (b) (4) container: The DS Reviewer concluded that the extractable/leachable studies conducted were appropriate, and that the (b) (4) compounds that were found (b) (4) posed a negligible safety risk; however, (b) (4) switched to (b) (4) containers based on the extractable/leachable results. The DS Reviewer concluded that a leachable study that looks for metal analysis by ICP-MS should be conducted, and that this issue may be addressed as a PMC (see DS PMC #8 above.)
- (6b-c) Quality and stability data of pancrelipase manufactured using the (b) (4) container: The DS Reviewer concluded that the release tests are within specifications but noted that a thorough characterization (i.e., impurity testing) was not performed; the DS Reviewer added that this is not considered a deficiency as (b) (4) has switched to (b) (4) containers. Regarding stability data in (b) (4), the DS Reviewer commented that enzyme activities and microbial counts are unaltered over (b) (4).
- (6d) Cleaning validation studies supporting re-use of (b) (4) containers: The DS Reviewer concluded that no visible pancrelipase API remains between runs and that total organic carbon and microbiological samples were well below specified limits.

Additional Pertinent Information (b) (4) Containers):

A summary of the DS Reviewer's assessment of the additional information provided by (b) (4) for (b) (4) containers is provided below.

- Quality and stability data of pancrelipase manufactured using (b) (4) containers: The DS Reviewer concluded that although a thorough characterization (e.g., impurity testing) was not performed, the stability study supports the notion that storage in the (b) (4) drums does not negatively impact product quality attributes. The DS Reviewer commented that enzyme activities and microbial counts were unchanged during a (b) (4) storage in the (b) (4) containers, noting that this is

longer than the allowed holding time of (b) (4). The DS Reviewer also commented that all specifications were met in four CoA's from lots manufactured using the (b) (4) containers.

- Cleaning validation studies supporting re-use of (b) (4) containers: The DS Reviewer concluded that no visible pancrelipase API remains between runs and that total organic carbon and microbiological samples were well below specified limits.

3.3.3 DP Issues (current cycle)

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

DP Postmarketing Commitments (PMC's):

DP items to be communicated to DCI (taken from Dr. Lacana's review) as postmarketing commitments (PMC's) are provided below. DCI provided the dates shown below on April 23, 2012. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

DP PMC #1: Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by December 2015

DP PMC #2: Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by July 2012

DP PMC #3: Establish an expiration date for the RP-HPLC column.

Final Report Submission by July 2015

DP PMC #4: Establish a primary reference standard against which future reference standards will be qualified.

Final Report Submission by December 2012

DCI's Response (to CR Letter Items #2 to #7):

A summary of the DP reviewer's assessment of the adequacy of DCI's response to Items #2 to #7 in the CR Letter to DCI (see Appendix 9) is presented below:

- (2) Request for prospective process validation reports: The DP Reviewer concluded based on a process validation summary report (PVR-003) (for three consecutive lots for the 8,000 and 16,000 lipase unit strengths) that the CR item has been resolved. The DP Reviewer commented that the process performed within all predefined acceptance criteria and there were no major protocol deviations, out of trend, or out of specification events. The DP Reviewer noted that the validation strategy is very similar to that used for other approved PEPs.
- (3) Release and stability acceptance criteria: The DP reviewer noted that the reason for the excursion in lipase activity of a particular lot (PC-6H05B) is not known, but this does not preclude approval as DCI has committed to continue evaluating stability results and trending data (see **DP PMC #1**). The DP reviewer also noted that the acceptance criteria for lipase activity have been (b) (4) slightly (from (b) (4) to (b) (4)), but should be further adjusted and (b) (4) as part of **DP PMC #1**.
- (4) Real-time stability data to support the requested expiry dating: The DP reviewer noted that the applicant has provided adequate data to support the requested MS-8 and MS-16 two-year expiry for the 100 and 250 capsule/bottle (b) (4).
 (b) (4)
 However, The DP reviewer recommended that the applicant commit to reevaluate the acceptance criteria for all assays and adjust appropriately when additional manufacturing experience is gained with this product. (See **DP PMC #2**.)
- (5) Reference standard qualification program: The DP Reviewer concluded that the applicant has improved the reference standard (RS) qualification program and has adequately addressed this item. The DP Reviewer noted the following: (a) Upper limits have been established for all specifications; (b) Acceptance criteria have been updated and are tighter than those used for product release; (c) A RP-HPLC method is now being used; and (d) The acceptance criteria are in line with the clinical trial lot (MS-16 6K09B). However, the DP reviewer noted that the RS qualification program does not include the establishment of a primary reference standard, and recommended that this issue be addressed as a PMC (see **DP PMC #4**).
- (6) Request for accelerated and/or stressed stability studies in annual stability program: The DP Reviewer concluded that this item has been adequately addressed as the applicant has updated the annual stability program to include an evaluation of the product when stored at ICH accelerated conditions (40°C/75%RH).
- (7) RP-HPLC assay used in release and stability testing: The DP reviewer determined that one part of this item (item c) was not adequately addressed, but did not preclude approval since it could be addressed as a PMC: (c) The DP reviewer noted that there has been an adequate evaluation of the percentage recovery of the protein samples, but not the column

lifetime; a column expiry should be established as part of a PMC (see **DP PMC #3**). The DP reviewer determined that the remaining parts of this item were adequately addressed: (a) A specification was established for the appearance of new peaks or for minor peaks. (b) Adequate justification and supporting data for the stability acceptance criteria were provided. (d) The Standard Operating Procedure (SOP) (TM-6803) for the RP-HPLC assay was provided, and was found to be adequate. (e) SOP TM-6803 has been updated to include the use of a drug product reference standard, a description of how impurities are quantified, and a specification that test samples are to be evaluated within (b) (4) of reagent preparation.

3.3.4 Microbiology Issues (current cycle)

A number of microbiology deficiency items were included in a deficiency letter sent to (b) (4) on October 27, 2010 (see Appendix 10).

In a review of microbiology issues (see Review by Stephen Langille dated January 31, 2012 filed under DMF (b) (4)), the Microbiology Reviewer concluded that the Responses to Deficiency Items #7 to #13 in the letter sent to (b) (4) October 27, 2010 were satisfactory. Vinayak Pawar (Microbiology Reviewer for NDA 22-175) stated in a memo dated February 3, 2012, that NDA 22-175 is recommended for approval as the product quality microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) have been adequately addressed.

In the CMC Summary Review by Emanuela Lacana (dated May 16, 2012 filed under NDA 22-175) and in a DMF Review (see Review by Richard Ledwidge dated May 15, 2012 filed under DMF (b) (4)), the CMC Reviewers concluded that the Response to Deficiency Item #14 in the October 27, 2010 letter to (b) (4) was satisfactory.

(b) (4) Response (to Deficiency Items #7 to #13):

A summary of Dr. Langille's assessment of the adequacy of (b) (4) response to Items #7 through #13 in the Letter to (b) (4) dated October 27, 2010 (see Appendix 10) is presented below.

- (7) Efforts to reduce the bioburden on incoming pancreas glands: (b) (4) received written confirmation from their slaughterhouses that the time between (b) (4) will be reduced to no more than (b) (4). The Microbiology Reviewer deemed the response to this item satisfactory, and commented that the hold times will be confirmed during slaughterhouse audits and technical visits.
- (8) Microbial limits specification: Microbiological specifications for the 1206 and 1208 manufacturing processes provided by (b) (4) were deemed satisfactory by the Microbiology Reviewer. One of the specifications was that TAMC must be no more than (b) (4).
- (9) Updated manufacturing procedures including timepoints for microbiological samples: The time limits and steps at which microbiological samples were to be collected were

provided by (b) (4) for the 1206 and 1208 processes. (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer.

- (10) Microbiological monitoring of pancreatin cake: The bioburden alert and action levels from the (b) (4) manufactured using the 1206 and 1208 processes were provided by (b) (4) and deemed satisfactory by the Microbiology Reviewer. (b) (4) also reiterated their commitment to test the bioburden of the (b) (4) from each drum immediately prior to (b) (4).
- (11) Microbiological alert and action levels: The action level provided by (b) (4) of no more than (b) (4) for the (b) (4) and (b) (4) samples was deemed satisfactory by the Microbiology Reviewer.
- (12) Commitment to clean processing equipment between batches: (b) (4) reiterated their commitment to clean all processing equipment between each batch with the exception of the (b) (4); this response was deemed satisfactory by the Microbiology Reviewer.
- (13) Updated microbial limits acceptance criteria for stability batches of DS: The Microbiology Reviewer noted that the current acceptance criteria for all stability samples are (b) (4), and stated that the response to this item is acceptable.

(b) (4) **Response (to Deficiency Item #14):**

Item #14 in the Letter to (b) (4) was related to the release test procedure for *Bacillus cereus*, and commitment to test each batch of DS for *Bacillus cereus* prior to release (see Appendix 10).

The Response to Deficiency Item #14 was discussed in the CMC Summary Review by Emanuela Lacana dated May 16, 2012 (filed under NDA 22-175), and in the DMF Review by Richard Ledwidge dated May 15, 2012 (filed under DMF (b) (4)).

Microbial Counts in Manufacturing: The CMC Secondary Reviewer noted that there are four points in the manufacturing process (b) (4) where samples are taken and microbial counts determined. The following was summarized from the literature by Richard Ledwidge⁶:

- Production of *Bacillus cereus* Diarrheal Enterotoxin (BDE) typically begins once cell density reaches 10^8 cells/ml in rich media (but has been shown to occur at a minimal level of 10^5 cells/gram).
- The FDA has set a risk threshold of 10^6 cells/g in food.
- Only middle and late exponential phases of proliferation show BDE production.

The CMC Secondary Reviewer noted that the in process limits were set as follows:

(b) (4)

⁶ Review by Richard Ledwidge filed under NDA 22-222 for Ultresa dated February 1, 2012.

The CMC Reviewers concluded that appropriate controls are in place to ensure no BDE production is taking place during manufacturing.

Bacillus cereus Enterotoxin: (b) (4) submitted assay development data (generated under contract by (b) (4)). The CMC Reviewers concluded the following based on the review of this data:

- The data indicated that the positive results in the ELISA assay used to detect B. cereus enterotoxin were false positives.
- The data supported the conclusion that the test approved to detect enterotoxin in food preparations was not suitable for pancrelipase samples.
- (b) (4) demonstrated that (b) (4) in pancrelipase samples is rapidly degraded by the proteases present in pancrelipase samples.

Overall Recommendation: The overall recommendation from the CMC Reviewers is that the concern about the risk of Bacillus cereus Enterotoxin contamination has been adequately addressed based on the improved microbial control strategy and the enterotoxin assay development data.

3.3.5 Facility Inspections (current cycle)

Recommendations from the Office of Compliance are as follows:

- Digestive Care Inc. (DCI) (NDA 22-175): “Acceptable” status in the Establishment Evaluation System (EES).⁷ The inspection of the DCI facility was conducted between February 23, 2012 and March 2, 2012.⁸ The Division of Compliance Information and Quality Assurance (DCIQA) database indicates that the date of the last Good Manufacturing Practice (GMP) inspection of DCI was March 2, 2012, and the agency position is that the firm is acceptable in the profile class for GMPs.
- (b) (4) (DMF (b) (4)): The inspection of the (b) (4) facility was conducted between (b) (4). The DCIQA database indicates that the date of the last GMP inspection of (b) (4) was (b) (4) and the agency position is that the firm is acceptable in the profile class for GMPs.

⁷ Email from Zhong Li (Chemist, Office of Compliance / Office of Manufacturing and Product Quality / Division of Good Manufacturing Practice Assessment / New Drug Manufacturing Assessment Branch) dated March 8, 2012.

⁸ Response to FDA-483 Inspectional Observations Issued 3/2/2012 Digestive Care Inc. FEI No. 1000136461

⁹ Email from Zhong Li (Chemist, Office of Compliance / Office of Manufacturing and Product Quality / Division of Good Manufacturing Practice Assessment / New Drug Manufacturing Assessment Branch) dated December 6, 2011.

3.4 Final Recommendation

An Approval Action is the final recommendation by CMC.

The DP and DS Reviews note that there are deficiencies identified in the NDA and in the DMF but these do not preclude approval of this application since these can be addressed as PMC's. (See Section 13.6 Postmarketing Commitments of this CDTL Review.)

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 Guidance¹⁰, 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 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 noted 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 noted 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 concluded 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 recommended an Approval action based on the non-clinical review of the information submitted in the NDA. Dr. Chakraborti additionally recommended that the proposed labeling be revised to include the following:

¹⁰ U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." <<http://www.fda.gov/cder/guidance/6275fnl.htm>> April 2006.

- 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)

4.2 Second 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 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 current review cycle.

The recommendations for labeling revisions from the initial review cycle were negotiated with the Applicant during the current review cycle. The labeling revisions included changes to the Pregnancy section and the Carcinogenesis, Mutagenesis and Impairment of Fertility section.

4.4 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/Toxicology discipline.

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 Pertzye in seven patients with EPI. Five capsules of Pertzye 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 Pertzye. 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) Pertzye 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 Pertzye 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 Second Review Cycle

5.2.1 Clinical Pharmacology

In the second 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. The clinical pharmacology reviewer noted that the Applicant addressed the issue of constructing the calibration curve for the lipase assay (CMC Deficiency #10 in the CR Letter dated August 27, 2009; Appendix 4), 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 (see Item #8 in the CR Letter dated January 27, 2011; Appendix 9):

- (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.

5.2.2 Biopharmaceutics

In response to deficiency item #20 in the first CR Letter (dated August 27, 2009; see Appendix 4), the applicant developed (b) (4) new MS-8, containing (b) (4) 8,000 USP lipase units, (b) (4). The applicant also provided dissolution testing data (including methodology and proposed specification) for each of the dosage strength formulations.

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:

- The applicant's proposed dissolution methodology is not considered optimal.
- 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.

Comments from the Biopharmaceutics Reviewer, although not approvability issues, were included as Additional Comments in the CR Letter (see Appendix 10), and the Applicant was requested to address these prior to resubmission.

5.3 Current Review Cycle

5.3.1 Clinical Pharmacology

DCI's Response (to CR Letter Item #8):

In the third review cycle, the Clinical Pharmacology reviewer determined that DCI adequately addressed CR Letter Item #8. A summary of the Clinical Pharmacology reviewer's assessment of DCI's response to parts a and b of Item #8 (see Appendix 9) is presented below:

- (8a) An adequate assay validation report with the assessment of in-process assay performance: The Clinical Pharmacology Reviewer concluded that the test method validation study report submitted (TMV-050) verified that the test method (TM-6013) for lipase activity was suitable for determining lipase activity of the PERTZYE enteric-coated microspheres when exposed to applesauce. The Clinical Pharmacology Reviewer noted that quality control (QC) samples to check in-process assay performance were run simultaneously. The Clinical Pharmacology Reviewer summarized the results as follows:
- Accuracy: The accuracy was determined by running the assays in duplicate at six concentrations of the assay range (6, 8, 10, 12, 14, and 16 U/mL). The accuracy was 92-107% for the QC samples (unexposed microspheres) and 98-102% for the microspheres exposed to 5mL of applesauce for 20 minutes. These results met the pre-specified acceptance criteria of an accuracy of 85-115% in accordance with the protocol.
 - Precision: The precision of the method was determined by running the assays in duplicate at six concentrations (6, 8, 10, 12, 14 and 16 U/mL) over a period of three days. The precision ranged from 1.4-2.5% CV for the concentrations tested for the QC Samples and 0.9-3.5% CV for the microspheres exposed to 5 mL of applesauce. All results for precision met the acceptance criteria of Relative Standard Deviation (RSD) less than 15% in accordance with the protocol.
- (8b) A complete food compatibility study report that would allow for a substantial clinical pharmacology review: The Clinical Pharmacology Reviewer concluded that the applesauce compatibility study report (RR-231) was comprehensive and allowed for a substantial clinical pharmacology review, and that the results of the study confirmed the stability of Pertzye microspheres exposed to applesauce at room temperature for 20 minutes. The Clinical Pharmacology Reviewer noted that the study was intended to demonstrate lipase stability versus time when the microspheres are exposed to

applesauce. At least three product batches were to be tested. The % of total lipase activity remaining after the microspheres are exposed to the applesauce for 20 minutes was determined as the percentage of the label claim. The Clinical Pharmacology Reviewer summarized the results as follows:

- Tested Lots: The mean lipase activity for each of the three lots ranged from 96-99%, thus meeting the acceptance criteria (not less than 90% of the label claim).
- QC Samples: The mean % lipase activity for the QC samples ranged from 97-98%, thus meeting the acceptance criteria (not less than 90% of the label claim).

5.3.2 Biopharmaceutics

DCI's Response (to Biopharmaceutics Additional Comments in CR Letter):

A summary of the Biopharmaceutics reviewer's assessment of the adequacy of DCI's response to Biopharmaceutics Additional Comments #1 to #4 included in the CR Letter to DCI (see Appendix 11) is presented below:

- (1) Low Recovery of Lipase Activity during Dissolution Testing: The Biopharmaceutics reviewer concluded that this issue has been resolved. The applicant had been requested to fully justify the proposed $Q = \text{(b) (4)}$ at 30 minutes, in particular to justify the use of assay method TM-6013 (which uses fortified intestinal fluid as a dissolution medium and olive oil as one of the added substrates) as opposed to the USP lipase assay method. Based on lipase activity results using method TM-6013 and another method (TM-6007), the Biopharmaceutics Reviewer determined that a mean correction factor (1.34) to recalculate the % of dissolved/release lipase activity at 30 minutes was acceptable. The Biopharmaceutics reviewer noted that based on the clinical lot (6K09B) and the stability lots of MS-16 and MS-8, there was a (b) (4) dissolved/release of lipase at 30 minutes.
- (2) Suggestion to Consider Use of the USP Dissolution Method: The Biopharmaceutics reviewer concluded that this issue should be addressed with a postmarketing commitment (PMC). The applicant had been suggested to consider conducting dissolution testing using the USP dissolution method (i.e., in the acid stage for one hour and then transferring the contents to the buffer stage). The Biopharmaceutics reviewer concluded that the applicant's proposed method is only acceptable on an interim basis, and that in the setting of the final method, the applicant should provide additional dissolution profile data (individual, mean, plots, $n = 12$) for both MS-8 and MS-16 strengths of the proposed Pertzye DR capsules. (See **Biopharm PMC#1** below.)
- (3) Dissolution Data/Profiles for the (b) (4) Dosage Strengths: The Biopharmaceutics reviewer concluded that the data submitted (comparative dissolution data/profiles) for the MS-8 and MS-16 capsule strengths support the Applicant's request for a biowaiver for the lower strength, MS-8. (b) (4)
- (4) Acceptance Criterion for Dissolution. The Biopharmaceutics reviewer concluded that this issue should be addressed with a postmarketing commitment (PMC). The applicant

had been requested to propose an acceptance criterion for the dissolution of the product. The Biopharmaceutics reviewer noted that the dissolution data from the stability batches (at time Zero) show that the mean percent of lipase dissolved for the MS-8 and MS-16 strengths is (b) (4) at 30 minutes and thus, the applicant's proposed acceptance criterion of Q (b) (4) at 30 minutes is not adequate. The Biopharmaceutics Reviewer concluded that the provided data support a dissolution criterion of Q = (b) (4) at 30 min, and recommended that implementation of this criterion should be on an interim basis, until sufficient data using the revised dissolution method are available for the setting of the final criterion. (See **Biopharm PMC#2** below.)

Biopharmaceutics Postmarketing Commitments (PMC's):

Biopharmaceutics items to be communicated to DCI (taken from Dr. Chen's review) as postmarketing commitments (PMC's) are provided below. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

Biopharm PMC#1: For the final dissolution method and acceptance criterion for Pertzye Delayed-Release Capsules:

- a. Follow USP method for dissolution testing, Method <711>, to incubate the product (n=12 capsule units) in the acid stage for 1 hour and then transfer the contents to the buffer stage. Collect a portion of buffer solution at several time points, e.g., 10 minutes, 20 minutes and 30 minutes. Proceed as directed to assay for lipase activity. Collect additional dissolution profile data from at least 3 production batches of each capsule strength containing either 8,000 or 16,000 USP units of lipase. Use the dissolution data from these production batches to set the buffer stage dissolution acceptance criterion for your product.
- b. Submit the final report with the complete dissolution data (individual, mean, min, max, and plots, n=12 capsule units) for both capsule strengths and a proposal for the buffer stage dissolution acceptance criterion for Pertzye Delayed-Release Capsules, as a prior approval supplement.

Final Report Submission by May 2013.

5.4 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology and Biopharmaceutics disciplines.

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 CDTL Review by Anil Rajpal dated August 27, 2009, the 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 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

*It should be noted that the formulation of Pertzye MS-8 in this study (submitted in the initial submission) is not the same as the Pertzye MS-8 formulation proposed in the second and current resubmissions.

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

A full listing of Pertzye 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 Pertzye 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 Pertzye 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 Pertzye 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 ≥ 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 ≥ 40% showed smaller increases in CFA after treatment with Pertzye 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 Pertzye MS-16 on CFA, it is not known whether Pertzye 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 Pertzye MS-8. It should be noted that the formulation of Pertzye MS-8 in this study (submitted in the previous submission) is not the same as the Pertzye MS-8 formulation proposed in the second and current resubmissions.

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 Pertzye MS-8 at an approximately 50% reduced lipase dose.

Dosage: The dosage of Pertzye 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 that of the 27 patients enrolled, seven patients did not meet entry criteria and 20 patients were randomized to treatment in the study. One patient did not participate in the second arm treatment and was excluded from the efficacy analysis; thus, 19 patients completed all study visits. One patient was non-compliant with the protocol specified diet and was identified by the sponsor as a major protocol violation.

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) showed that there was little difference (not statistically significant) between the mean CFA for Pertzye MS-8 of 77 and the mean CFA for usual enzyme of 76. A per-protocol (PP) analysis showed a mean CFA for Pertzye MS-8 of 82 and a mean CFA for usual enzyme of 76. 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 (%)	77.4 (14.5)	75.6 (9.8)	0.44
PP Population (n=18)			
CFA (%)	81.8 (10.9)	75.9 (9.2)	0.01

* 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 Second Review Cycle

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

In response to the clinical deficiency item in the first CR Letter (Item #20; see Appendix 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 Current Review Cycle

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

It should be noted that in the current submission, the Applicant is pursuing approval of (b) (4) the MS-8 and MS-16 capsule strengths (b) (4)

7.4 Final Recommendation

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

8. Safety

The reader is referred to the CDTL Review by Anil Rajpal dated August 27, 2009, the Clinical Review by Marjorie Dannis dated August 27, 2009, and the Clinical Reviews of Safety Updates by Marjorie Dannis dated January 14, 2011, and December 23, 2011, 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.^{11,12,13} (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.
- 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.^{14,15} (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

¹¹ 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.

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 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.

¹⁴ Antiviral Drugs Advisory Committee (December 2, 2008);

<<http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs>>

¹⁵ Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

8.1 Initial Review Cycle

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

Exposure

The safety population includes 262 subjects exposed to Pertzye 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 Pertzye.)

The safety of Pertzye 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			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)
		Units/kg/day ^d	5,811	4,096
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 Pertzye formerly marketed as "Pancrecarb." However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b)(4) Pertzye capsules were shipped to wholesalers. If the usual range of daily intake of Pertzye is 10 to 20 capsules, this would represent approximately (b)(4) patients currently being treated with Pertzye 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 Pertzye MS-8 (see Clinical Review). No other deaths were reported during any other study with Pertzye.

SAEs: Three Pertzye 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 Pertzye. The long-term study (091897) contributed 13 of the 18 Pertzye 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 (Pertzye 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 (Pertzye 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 Pertzye 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 Pertzye 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 Pertzye 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: Pertzye 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 Pertzye, 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 Pertzye 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 Second 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 Current Review Cycle

The clinical reviewer stated in a memo dated December 23, 2011, that since the time of the previous resubmission (February 2010), "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." Thus, the clinical reviewer's conclusions have not changed from the conclusions stated in the original review dated August 27, 2009.

8.4 Final Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The application was presented to the Pediatric Research Committee (PeRC) during the current review cycle on April 4, 2012. In addition, a consult with the Pediatric Maternal Health Staff (PMHS) was obtained prior to the meeting with PeRC in order to determine how to address the issue of dosing recommendations for infants and lower body weight children given the limitations of the available dosage strength formulations of Pertzye.

10.1 Pediatric Research Committee (PeRC)

The schema below was proposed at the Pediatric Research Committee (PeRC) on April 4, 2012 (with the corresponding rationale):

(1) Waiver for:

- ages 0 to < 1 month

Rationale: Necessary studies are impossible or impracticable because patients are usually not diagnosed before the age of 1 month, so there would not be enough eligible patients in this age range to study.

(2) Deferral for:

- ages ≥ 1 month to < 12 months;
- ages ≥ 12 months to < 4 years (weighing less than 8 kg); and
- ages ≥ 4 years to < 17 years (weighing less than 16 kg)

Rationale: Development of an age-appropriate formulation is needed. See Section 10.2 below.

(3) Completed for:

- ages ≥ 12 months to < 4 years (weighing 8 kg or more); and
- ages ≥ 4 years to < 17 years (weighing 16 kg or more)

Rationale: Each of the PEPs was unapproved prior to being submitted under NDA; thus, existing labels for the PEPs not submitted under NDA are not viewed as valid. One body of evidence (a range of study types using all formulations of the pancreatic enzymes) was used to create class labeling. As this is new labeling for each of the PEPs, and because the labels did not previously exist, the studies needed to fulfill PREA are considered as having been completed.

It should be noted that the deferral for patients ages ≥ 1 month to < 12 months, ages ≥ 12 months to < 4 years (weighing less than 8 kg), and ages ≥ 4 years to < 17 years (weighing less than 16 kg) does not require additional clinical studies; rather, the deferral for this age category is for the development of an age-appropriate formulation (see Section 10.2 below). Such a formulation will allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

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

A related point that deserves mention is that there is no “extrapolation” of efficacy data from one age category to another. Rather, the extensive data from studies in the published literature with a variety of PEP formulations across pediatric age groups constitutes evidence of efficacy for PEPs in the pediatric population; evidence of efficacy for the particular formulation (i.e., Pertzye) comes from the randomized double-blind placebo-controlled cross-over study using that formulation (i.e., Study 06-001) regardless of whether it was conducted in a pediatric population, an adult population, or a population that included both adult and pediatric patients. In effect, Study 06-001 can be considered to be a “bridging study” to the existing body of evidence from the literature for a range of pancreatic enzyme formulations.

10.2 Consult with Pediatric and Maternal Health Staff (PMHS)

The Pediatric and Maternal Health Staff (PMHS) was consulted because the smallest dosage strength formulation of Pertzye contains 8,000 USP units of lipase and dosing recommendations in the label may not be feasible for an infant and for lower body weight children as the capsule contents would have to be split into small fractions (i.e., splitting the dose in one-fourth or smaller fractions).

The PMHS reviewer (Elizabeth Durmowicz) provided recommendations for the labeling, primarily in the Dosage and Administration section. The PMHS reviewer noted the following:

- (1) Dosing to infants may not be feasible with the current smallest dosage strength formulation of 8,000 USP units of lipase as the contents would have to be split into one-quarter or smaller fractions.
- (2) For children 12 months and older to less than 4 years, the age and weight based CFF dosing guidelines recommend 1000 USP units of lipase per kg body weight per meal; thus, dosing to children less than 8 kg may not be feasible as the dose would have to be split in half for meals and in fractions smaller than one-half for snacks.
- (3) For children 4 years and older, the age and weight based CFF dosing guidelines recommend 500 USP units of lipase per kg body weight per meal; thus, dosing to children less than 16 kg may not be feasible as the dose would have to be split in half for meals and in fractions smaller than one-half for snacks.

The following label revisions are recommended:

- (1) (b) (4) should be deleted.
- (2) For children older than 12 months to less than 4 years, a statement should be added that children weighing under 8 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.
- (3) For children 4 years and older, a statement should be added that children weighing under 16 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

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. Pertzye 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, Pancreaze, Ultresa, and Viokace 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. Since that time, two more PEPs (Ultresa and Viokace) were approved. Thus, with the approval of Pertzye, a drug shortage does not appear to be likely.

11.4 Administration via Gastrostomy Tubes


PEPs, including Pertzye, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Pertzye via gastrostomy tubes, the Applicant has committed to conducting *in vitro* testing (see Section 13.6).

12. Labeling


12.1 Proprietary name

12.1.1 Initial Review Cycle

In the initial review cycle, the name “Pancrecarb” was submitted. 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 objected 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 (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 indicated 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.

12.1.2 Second Review Cycle

The proprietary name “Pertzye” was deemed acceptable shortly before the start of the second 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 DMEPA (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 Pertzye is not vulnerable to name confusion that could lead to medication errors.

12.1.3 Current Review Cycle

In the current review cycle, DMEPA concluded that the proprietary name of “Pertzye” was acceptable. Please see the DMEPA Proprietary Name Review by Manizheh Siahpoushan dated February 10, 2012 and the DMEPA Label and Labeling Review by Manizheh Siahpoushan dated February 23, 2012 for complete information.

In the February 10, 2012 Proprietary Name Review, the reviewer concluded that based on the Proprietary Name Risk Assessment findings, the proposed name, Pertzye, is not vulnerable to name confusion that could lead to medication errors.

In the February 23, 2012 Label and Labeling Review, the reviewer identified areas of needed improvement in order to reduce the potential for medication errors. To address these issues, the DMEPA Reviewer provided:

- (a) Comments regarding the Physician Labeling and Medication Guide: These were negotiated with the Applicant during labeling meetings.
- (b) Comments regarding Carton and Container Labeling: Each of the issues was adequately addressed in responses from the Applicant.

12.1.4 Final Recommendation

The proprietary name “Pertzye” was deemed acceptable as per the Proprietary Name Request Conditionally Acceptable Letter sent to Digestive Care, Inc. dated February 10, 2012.

12.2 Division of Drug Marketing, Advertising, and Communications (DDMAC) / Office of Prescription Drug Promotion (OPDP) 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.

Second Review Cycle: DDMAC had no concerns regarding the proposed proprietary name “Pertzye” 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.

Current Review Cycle: The Office of Prescription Drug Promotion Comments (OPDP) (formerly DDMAC) had no concerns regarding the proposed proprietary name “Pertzye” 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 Manizheh Siahpoushan dated February 10, 2012.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The Applicant was requested to revise the label and medication guide to be consistent with the corresponding sections for the other drugs in the class that were recently approved (Creon, Zenpep, Pancreaze, Ultresa, and Viokace). In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMEPA Label and Labeling Review, the DMPP Patient Labeling Review, the DTP Carton and Container Label Review, the OPDP Labeling Review, and the SEALD Labeling Review. The reader is referred to each of these reviews for complete information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

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

13.2 Risk Benefit Assessment

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

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

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

REQUIRED PEDIATRIC ASSESSMENTS

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

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

We note that you have fulfilled the pediatric study requirement for patients greater than 1 year to less than 4 years (weighing 8 kg or more) and patients 4 to 17 years (weighing 16 kg or more) for this application.

The pediatric requirement for patients 1 month to 1 year, patients greater than 1 year to less than 4 years (weighing less than 8 kg), and patients ages 4 to 17 years (weighing less than 16 kg) is not fulfilled due to the lack of an age appropriate formulation.

We are deferring submission of your pediatric study for patients 1 month to 1 year, patients greater than 1 year to 4 years (weighing less than 8 kg), and patients 4 to 17 years (weighing less than 16 kg). The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This requirement is listed below.

PMR #1: Deferred requirement for development of an age appropriate formulation for Pertzye (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by June 30, 2014.

Reports of this required pediatric postmarketing study must be submitted as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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 serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients.

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

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

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

The timetable you submitted on May 15, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 2013
Study Completion: July 2023
Final Report Submission: July 2024

PMR #3: An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Pertzye (pancrelipase) Delayed-Release Capsules compared with an appropriate control group.

The timetable you submitted on May 15, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 2013
Study Completion: July 2018
Final Report Submission: July 2019

Submit the protocols to your IND 045223, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

Clinical:

Clinical PMC#1: Perform in vitro studies to determine the feasibility of administering the contents of Pertzye (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.
Final Report Submission by June 2013.

Biopharmaceutics:

Biopharm PMC#1: For the final dissolution method and acceptance criterion for Pertzye Delayed-Release Capsules:

- a. Follow USP method for dissolution testing, Method <711>, to incubate the product (n=12 capsule units) in the acid stage for 1 hour and then transfer the contents to the buffer stage. Collect a portion of buffer solution at several time points, e.g., 10 minutes, 20 minutes and 30 minutes. Proceed as directed to assay for lipase activity. Collect additional dissolution profile data from at least 3 production batches of each capsule strength containing either 8,000 or 16,000 USP units of lipase. Use the dissolution data from these production batches to set the buffer stage dissolution acceptance criterion for your product.
- b. Submit the final report with the complete dissolution data (individual, mean, min, max, and plots, n=12 capsule units) for both capsule strengths and a proposal for the buffer stage dissolution acceptance criterion for Pertzye Delayed-Release Capsules, as a prior approval supplement.

Final Report Submission by May 2013.

Drug Product:

DP PMC #1: Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by December 2015

DP PMC #2: Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by July 2012

DP PMC #3: Establish an expiration date for the RP-HPLC column.

Final Report Submission by July 2015

DP PMC #4: Establish a primary reference standard against which future reference standards will be qualified.

Final Report Submission by December 2012

Drug Substance:

Viral

- DS PMC #1: Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.
Final Report Submission by September 1, 2012
- DS PMC #2: Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).
Final Report Submission by March 1, 2013
- DS PMC #3: Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.
Final Report Submission by March 1, 2013
- DS PMC #4: Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program should include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.
Final Report Submission by May 15, 2013
- DS PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria should be submitted to the Agency.
Final Report Submission by April 15, 2013
- DS PMC #6: Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
Final Report Submission by June 1, 2012
- DS PMC #7: Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.
Final Report Submission by March 15, 2013

Non-Viral:

- DS PMC #8: Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.
Final Report Submission by June 1, 2012

DS PMC #9: Revise release specifications after 30 lots of drug substance 1206 and 1208 lots have been manufactured.
Final Report Submission by May 15, 2013

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995¹⁶) 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. 2002¹⁷ 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. 1997¹⁸ 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

¹⁶ 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.

¹⁷ 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.

¹⁸ 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

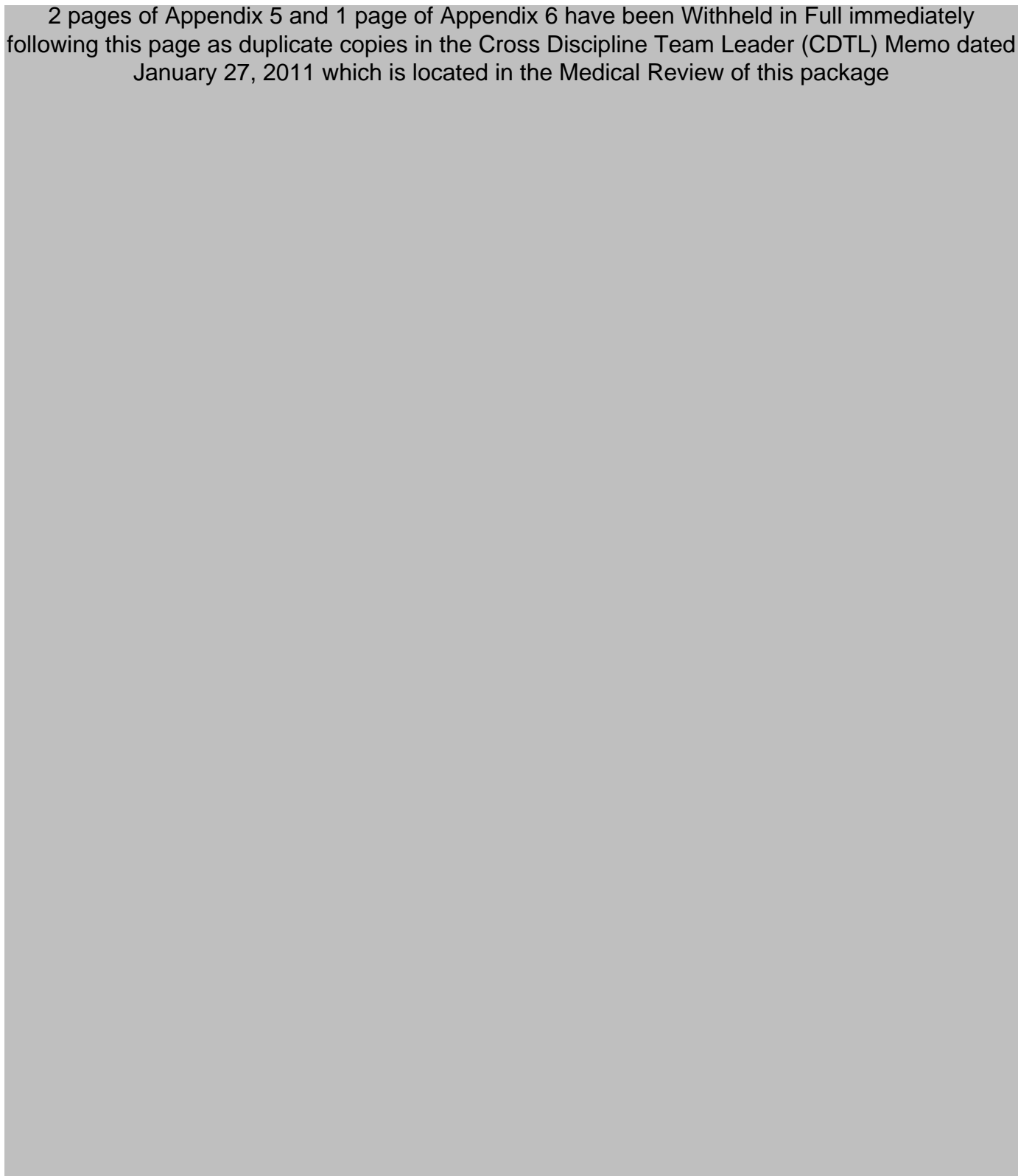
Deficiencies from the CR Letter (NDA 22-175) dated August 27, 2009 are provided below:

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 – August 28, 2009

2 pages of Appendix 5 and 1 page of Appendix 6 have been Withheld in Full immediately following this page as duplicate copies in the Cross Discipline Team Leader (CDTL) Memo dated January 27, 2011 which is located in the Medical Review of this package



**APPENDIX 7: Summary of Observations Cited in FDA Form
483 (issued to DCI, to (b) (4) and to (b) (4))**

(b) (4)

2 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

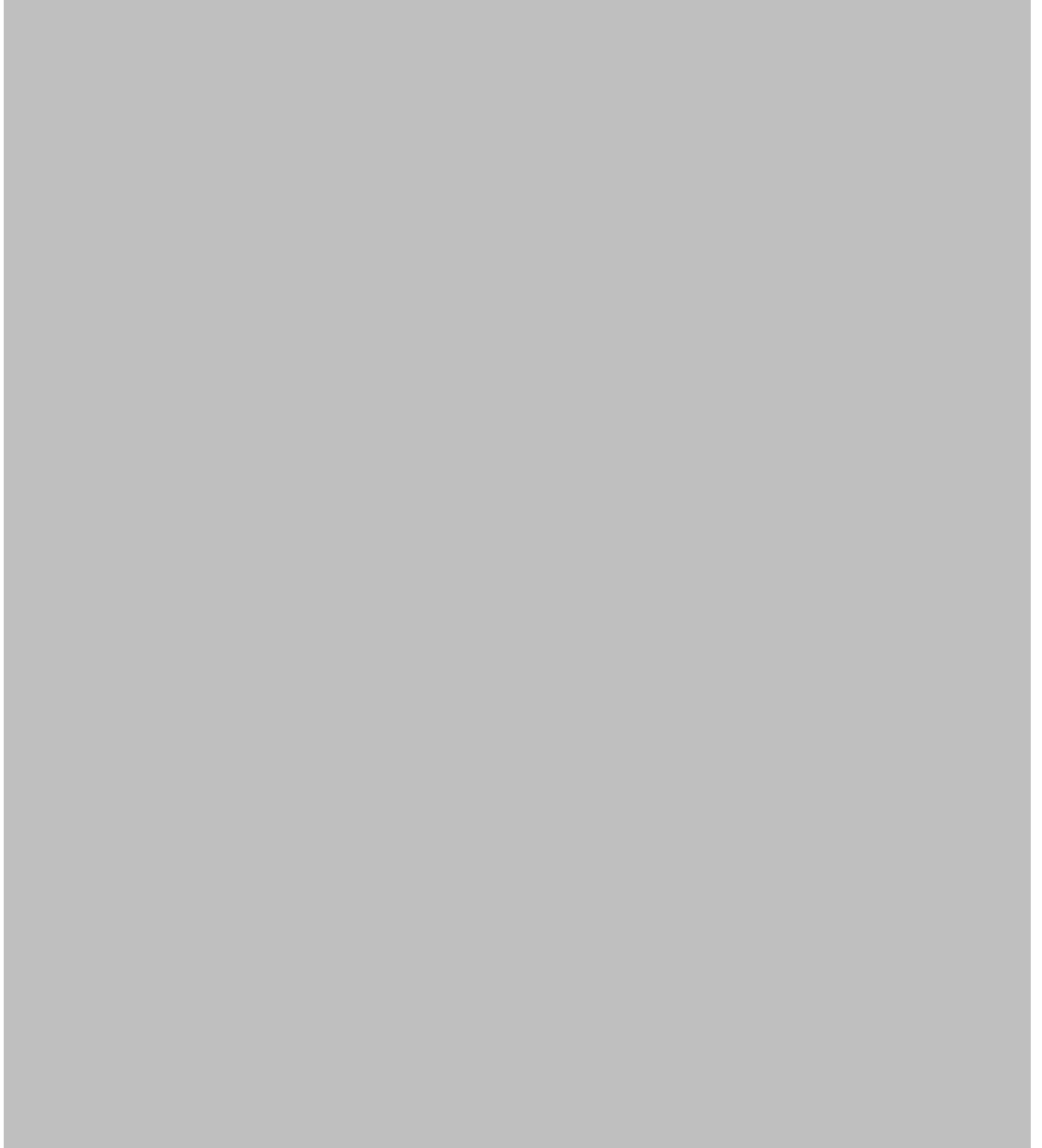
APPENDIX 8: Summary of HHE Review – February 23, 2010

This Appendix is a duplicate copy in the Cross Discipline Team Leader (CDTL) Memo dated January 27, 2011 which is located in the Medical Review of this package

APPENDIX 9: NDA Deficiency Items – Second Action

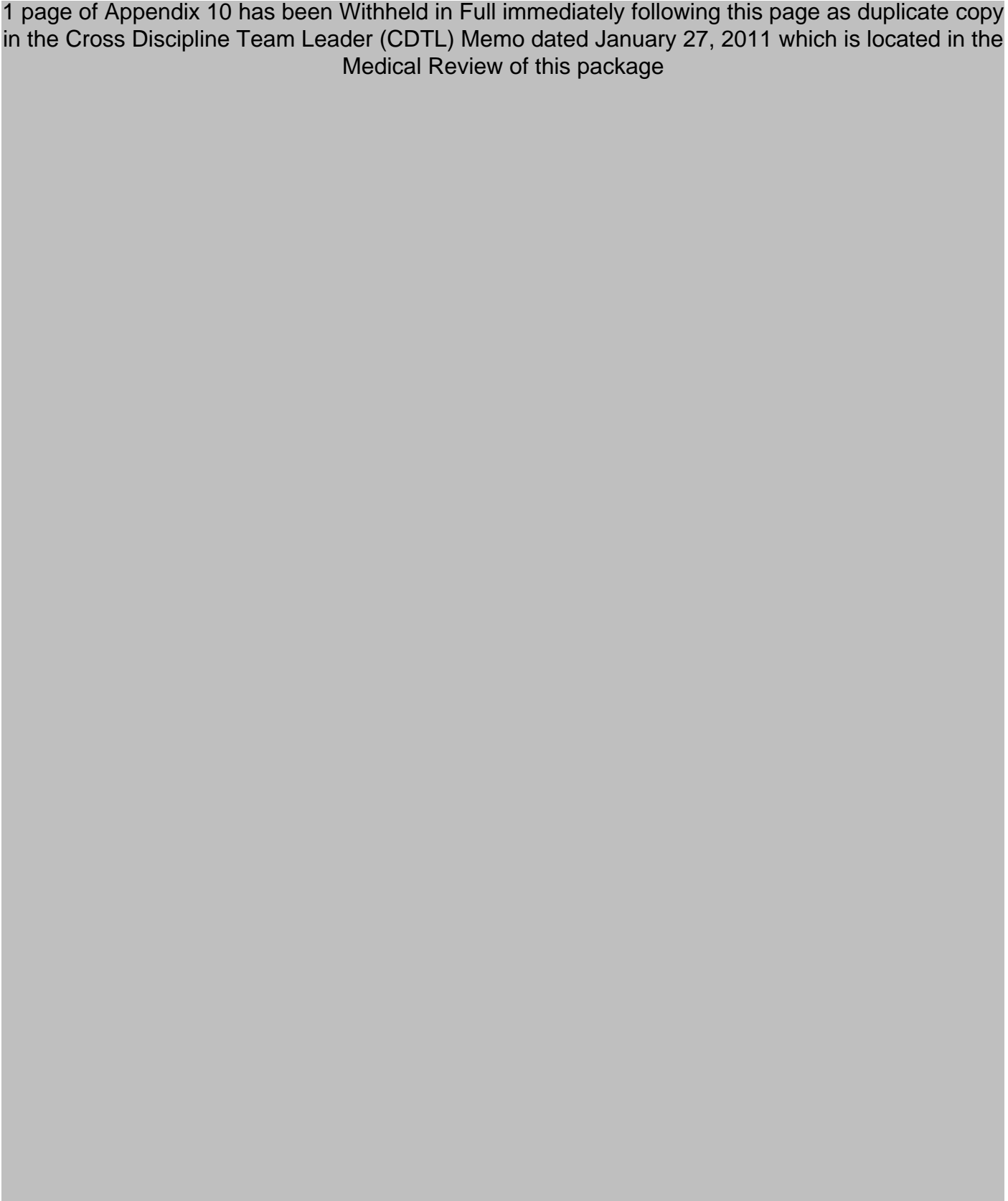
Deficiencies from the CR Letter (NDA 22-175) dated January 27, 2011 are provided below:

3 pages of Appendix 9 have been Withheld in Full immediately following this page as a duplicate copy of the Other Action letter dated 01/27/2011 which can be found in this approval package



APPENDIX 10: DS Deficiency Items – October 27, 2010


1 page of Appendix 10 has been Withheld in Full immediately following this page as duplicate copy in the Cross Discipline Team Leader (CDTL) Memo dated January 27, 2011 which is located in the Medical Review of this package



APPENDIX 11: Biopharmaceutics Additional Comments – Second Action

Additional Comments that were included in the CR Letter (NDA 22-175) dated January 27, 2011 are provided below:

This Appendix is a duplicate copy of the Other Action letter dated 01/27/2011 which can be found in this approval package



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
05/17/2012