CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 21, 2009
From	Anil Rajpal, MD, Acting Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-210
Applicant	Eurand Pharmaceuticals, Inc.
Date of Submission	December 22, 2008; Received December 23, 2008
PDUFA Goal Date	September 23, 2009 (includes three-month extension for a major amendment)
Proprietary Name / Established (USAN) names	Zenpep® pancrelipase
Dosage forms / Strength	Zenpep® (pancrelipase) delayed release-capsules for oral administration, in USP units ▪ Zenpep 5,000 lipase/17,000 protease/27,000 amylase ▪ Zenpep 10,000 lipase/34,000 protease/55,000 amylase ▪ Zenpep 15,000 lipase/51,000 protease/82,000 amylase ▪ Zenpep 20,000 lipase/68,000 protease/109,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Approval under 21 CFR 314

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1. Introduction

This resubmission, received December 23, 2008, is a complete response to the Approvable (AE) Letter sent by the Division on June 16, 2008, and represents the second review cycle for Zenpep (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP); Zenpep is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

In the first review cycle, deficiencies were identified by the Chemistry, Manufacturing, and Controls (CMC) discipline, and by the Clinical Pharmacology discipline. CMC deficiencies in the AE letter were related to: (1) process validation; (2) enteric coating; (3) stability data; (4) storage conditions; (5) drug substance (separate letter with 18 items sent to the DMF holder; included viral issues); (6) olive oil qualification; (7) drug product acceptance criteria; (8) RP-HPLC assay validation; (9) qualification of the reference standard; and (10) USP lipase reference standard used. A clinical pharmacology deficiency was the eleventh item in the AE letter: (11) a clarification about *in vitro* stability data.

No clinical deficiencies were identified in the first review cycle. The initial submission contained results from three clinical studies: (a) pivotal study (EUR-1008-M; randomized double-blind cross-over study; n=34); (b) supportive study (EUR-1009-M; open-label; uncontrolled; n=19); and (c) bioavailability study (PR-001; n=11). The current submission contains a safety update to March 30, 2008.

It should be noted that during the current review cycle, information became available that the Applicant was continuing to market another pancrelipase product "in association with IND 70,563 and NDA 22-210." Complete safety information was required to be submitted for the unbranded pancrelipase product; this was received on June 15, 2009 and constituted a major amendment that led to the three-month extension of the PDUFA date.

The primary emphasis of this memorandum is on the issues to be resolved in the current review cycle.

2. Background

2.1 Clinical Background

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

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause.

Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

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

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

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

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

Thus, there is only one approved PEP, Creon, that is currently commercially available in the US.

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

Federal Register Notices: Over the past many years, the FDA has published a number of notices in the Federal Register (FR) with the aim of requiring all marketed PEPs to have undergone the NDA application and review process. This is largely to address variations in formulation, dosage, and manufacturing processes, both between different PEPs and within individual PEP brands. Recent FR notices for PEPs are summarized in the table below; a more complete history is provided in the review by Dr. Anne Pariser dated June 16, 2008.

[1] 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.
[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: ▪ open IND by April 28, 2008, ▪ NDA submitted by April 28, 2009, and ▪ approved NDA by April 28, 2010.

Above is summarized from Anne Pariser's CDTL review dated June 16, 2008.

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

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

(1) Risk of Fibrosing Colonopathy: To address the concern that the risk of FC may be increased with high dose exposure to PEPs, a Medication Guide that informs patients of the risk of FC is part of the REMS for Creon. (See also Section 2.1 and Appendix 1.)

(2) Risk of Transmission of Viral Disease to Patients: There is a concern that because Creon and other PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[4,5] To address the concern about the theoretical risk of viral transmission, a Medication Guide that informs patients of the theoretical risk of viral transmission is part of the REMS for Creon. (See also Drug Product and Drug Substance Reviews.)

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

[5] Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

2.2.2 Regulatory History of Zenpep

The table below summarizes the regulatory activity of Zenpep for EPI; a more complete summary of the period before the Approvable Action is provided in the review by Dr. Anne Pariser dated June 16, 2008.

Table 2. Pertinent Regulatory History of Zenpep

Date	Action
November 2005	Original IND submission
January 2007	Fast Track Designation
December 2007	NDA 22-210 submitted for Zenpep
June 2008	Approvable Action
July 2008	Meeting with the Sponsor to discuss items in the Division's Approvable Letter
December 2008*	Class II Resubmission – Complete Response to Approvable Letter

*Response to Approvable Letter submitted in September 2008 deemed incomplete due to Item #5 (Nordmark DMF) deficiency
History prior to approvable action summarized from Anne Pariser's CDTL review dated June 16, 2008.

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

- Cross Discipline Team Leader Review by Anne Pariser, dated June 16, 2008
- Clinical Review by Marjorie Dannis, dated June 15, 2008
- Statistical Review by Freda Cooner, dated June 9, 2008

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

- Approvable Letter sent to Eurand Pharmaceuticals, Inc. dated June 16, 2008
- Letter sent to Nordmark Arzneimittel GmbH & Company, KG dated June 13, 2008 (Master File #7090)

2.3 Current Submission

The NDA resubmission was dated December 22, 2008, and it was received on December 23, 2008. It was classified as a six-month resubmission with a PDUFA deadline of June 23, 2009; because of a major amendment received on June 15, 2009, the PDUFA date was extended to September 23, 2009.

It should be noted that during the current review cycle, information became available that the Applicant was continuing to market another pancrelipase product "in association with IND 70,563 and NDA 22-210." Complete safety information was required to be submitted for the unbranded pancrelipase product; this was received on June 15, 2009 and constituted a major amendment that led to the three-month extension of the PDUFA date. (See Clinical Review of Safety Update by Marjorie Dannis.)

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:

- Clinical Review of Safety Update by Marjorie Dannis, dated August 12, 2009
- Clinical Pharmacology Review by Tien-Mien Chen, dated August 17, 2009
- DTP Reviews of CMC by Howard Anderson:
  - Drug Product Review, dated August 18, 2009
  - Drug Substance Review (review of DMF), dated August 18, 2009
- DMEPA Reviews by Deveonne Hamilton-Stokes:
  - Proprietary Name Review, dated July 30, 2009
  - Labeling Review, dated May 5, 2009
  - Proprietary Name Review, dated March 6, 2009
- DRISK Reviews:
  - Proposed REMS Review by Jessica Diaz, dated July 22, 2009
  - Patient Labeling and Medication Guide Review by Robin Duer, dated July 19, 2009
- DTP Carton and Container Label Review by Kimberly Rains, dated June 5, 2009
- DDMAC Labeling Review by Shefali Doshi, dated June 15, 2009
- SEALD Labeling Review by Jeanne Delasko, dated June 11, 2009

The reviews should be consulted for more specific details of the application. The reader is also referred to the CDTL Review dated June 16, 2008, for the initial review cycle, as well as to the primary review documents from that cycle.

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 CDTL Review by Anne Pariser dated June 16, 2008, and the Drug Product and Drug Safety Reviews by Howard Anderson dated August 18, 2009 for complete information.

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

Overview of Virology: Given the source of the material, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known

to be present in swine include enveloped, non-enveloped, and emerging viruses listed and considered in detail in the virology review. (b) (4) 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 Eurand in a process that entails (b) (4) Zenpep capsules contain 5,000, 10,000, 15,000 and 20,000 USP units (U) lipase. The 10,000, 15,000, and 20,000 U capsules contain identical pancrelipase formulated beads; the 10,000, 15,000, and 20,000 U capsules contain enteric-coated cylindrical mini-tablets having a diameter of (b) (4) mm and a thickness of 2.2 mm. The 5,000 U capsule beads ("small coated beads") are prepared with approximately dose proportional pancrelipase excipients; the 5,000 U capsules contain slightly smaller mini-tablets having a diameter of (b) (4) mm and a thickness of (b) (4) mm. The smaller size beads in the 5,000 U strength capsules offer the potential advantage of administration to young children by sprinkling the beads onto food. Stability studies with small beads mixed in foods (e.g., applesauce, pudding) support the use of various foods to administer the small beads (stability for up to 60 minutes). (See Section 5 Clinical Pharmacology.)

Packaging: The capsules are packaged in amber glass bottles. Each bottle contains a desiccant package. Zenpep is presented in four strengths, based on the lipase activity content: 5,000, 10,000, 15,000, and 20,000 USP units.

3.1 Initial Review Cycle

In the initial review cycle, the Drug Product review and Drug Substance review was conducted by Howard Anderson, the Virology review was conducted by Ennan Guan, and the Microbiology review was conducted by Stephen Langille. Each of these reviews was summarized in the CDTL review by Anne Pariser. (Please refer to the CDTL review, and each of the individual reviews for more information.)

An Approvable (AE) action was recommended from the Drug Substance, Virology, and Drug Product reviews; an Approval (AP) action was recommended from the Microbiology Review.

The deficiencies identified by the Virology, Drug Substance, and Drug Product Reviewers are summarized below.

Viral DS Issues

The overall assessment of the virology reviewer was that although the manufacturing process may provide for an acceptable capacity for viral inactivation of enveloped viruses and inadequate viral inactivation for non-enveloped viruses, without additional data (e.g., assay validation characteristics), the results are not assured. Infectivity testing by cell-based assays for non-enveloped viruses was also performed. Using these assays, Nordmark showed that negative infectivity results were observed for all viruses tested, except for PPV, PCV1, and PCV2. HEV was not detected, but DTP did not feel the results of this test were reliable. DTP's assessment of Nordmark's routine viral testing plan, which plans to routinely test for a limited number of viruses (PPV, HEV and PEV9) was that the plan is inadequate, and did not sufficiently address risk. DTP recommended that the testing plan include routine testing of all viruses thought to have the capacity to infect humans, to routinely test infectivity of PCV 1 and 2, and to address risk mitigation for emerging viruses, animal disease surveillance, and sanitizing procedures for equipment.

Deficiency items for viral issues that were sent to Nordmark were related to (see final wording of Items #1 to #5 in letter to Nordmark in Appendix 2): (1) risk mitigation for adventitious agents; (2) viral inactivation studies; (3) validation of PCR tests; (4) validation of viral infectivity assays; and (5) specifications for adventitious agents.

Non-Viral DS Issues

The DS reviewer noted that characterization of the enzymes contained in the DS, including assays for amylase, lipase, protease (e.g., for a number of individual proteases, such as (b) (4) was performed. Detailed descriptions and validation reports for the analytical methods and enzyme assays used also were provided. The overall findings of the DS reviewer were that there were a number of deficiencies identified for the DS, including deficiencies in DS manufacturing and controls.

Deficiency items for non-viral DS issues that were sent to Nordmark were related to (see final wording of Items #6 to #18 in letter to Nordmark in Appendix 2): (6) USP lipase, amylase, and protease reference standards; (7) specification for total starting gland weight; (8) plans to re-examine the production process; (9) rejected batches may not be reworked or reprocessed; (10) (b) (4) (11) release specifications; (12) HPLC assay validation; (13) specification for water content for release testing: (14) (b) (4) specification for DS release; (15) demonstration of predicted lipase activity; (16) olive oil qualification; (17) DS label; and (18) storage conditions and expiration date.

DP Issues

The DP reviewer noted that characterization of physicochemical and biological properties of lipase, protease, and amylase activities have been carried out on clinical trial lots of DS and DP. Validation of analytical methods has been provided, and in general, validation is acceptable and data are presented to support that enzyme reactions are linear with respect to time and specific activity is measured. Spiking DS with excipients demonstrate that excipients do not affect the performance of enzyme activity assays; however, further

information is required for the lipase assay. Stability data to support 18 months of product storage are also provided. The overall findings of the DP reviewer were that there were a number of deficiencies identified for the manufacture of DP.

CMC deficiencies in the AE letter were related to (see final AE Letter wording in Appendix 3): (1) process validation; (2) enteric coating; (3) stability data; (4) storage conditions; (5) drug substance (separate letter with 18 items sent to the DMF holder; included viral issues); (6) olive oil qualification; (7) drug product acceptance criteria; (8) RP-HPLC assay validation; (9) qualification of the reference standard; and (10) USP lipase reference standard used.

3.2 Current Review Cycle

In the current review cycle, both the reviews of Drug Product and Drug Substance were conducted by Howard Anderson. (The reader is referred to the Drug Substance Review dated August 18, 2009, and the Drug Product Review dated August 18, 2009, for complete information.)

A review by the Microbiology discipline was not conducted during the current cycle because the microbiology reviewer recommended an Approval Action in the first cycle. A separate review by the Virology discipline was not conducted in the current review cycle; virology issues are included in the review of Drug Substance.

Viral DS Issues

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

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

(1) Risk mitigation plan for adventitious agents. Each of the parts of this item was adequately addressed: (a) The plan for disease surveillance includes a provision that [redacted] (b) (4) thus allowing sufficient time to prevent the release of potentially contaminated glands. (b) [redacted] (b) (4) (d) It was confirmed that the porcine glands are generally not considered food items, but are derived from animals fit for human consumption. (e) The manufacturer stated that according to EU regulations, imported animals from Canada or the US must be accompanied by a health certificate (documenting that the animals remained in the territory since birth or at least three months before slaughter), and importation of living pigs is restricted to a limited number of countries (Canada, Switzerland, Chile, Iceland, and New Zealand); the manufacturer also noted that importation of living pigs for slaughtering is not a common event. The response was deemed adequate by the DS reviewer. The DS reviewer noted that on

inspection, Nordmark indicated that Eurand specifies that pancreatic glands be obtained only from swine raised in the US or Canada. (f) Details of the gland qualification program were provided, and were deemed adequate by the DS reviewer.

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

(3) Validation Characteristics of PCR tests. A PMC is recommended; the DS reviewer recommends that Nordmark should increase the sensitivity of the viral PCR assays for DS release testing as a PMC. The DS reviewer notes that critical validation parameters (e.g., sensitivity, linearity, precision, and recovery) of the PCR tests to detect EMCV, HEV, PEV9, Reo1/3, Rota A, Flu A, VSV-IND, and VSV-NJ genome equivalents were provided. The DS reviewer further notes that the infectious assay sensitivity is equivalent to that of Creon manufactured by Solvay.

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

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

incoming glands to estimate the potential starting levels for the enveloped viruses. The DS reviewer determined that the remaining part (c) of this item was adequately addressed: (c) Because PPV genome equivalents measurements are not correlated with infectivity, the manufacturer eliminated this measurement.

Non-Viral DS Issues

The DS reviewer noted that a deficiency exists, but it does not preclude approval of the application since it can be addressed as a PMC. (See Drug Substance Review by Howard Anderson for complete information.)

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

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

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

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

(9) (b) (4)

(10) (b) (4)

(11) (b) (4)

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

(13) Specification for water content for release testing: The manufacturer was requested to establish a specification for water content for DS release and stability testing. The response is adequate as the current test method provides an accurate measurement of water content in the active pharmaceutical ingredient (API).

(14) (b) (4)

(15) Demonstration of predicted lipase activity (b) (4)

The response is adequate as Nordmark has performed the requested characterization studies to demonstrate that lipase-inhibitory compounds are not present in the API.

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

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

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

under appropriate conditions. The DS reviewer concluded that the response is adequate.

DP Issues

The DP reviewer noted that a deficiency exists, but it does not preclude approval of the application since it can be addressed as a PMC. (See Drug Product Review by Howard Anderson for complete information.)

A summary of Items #1 to #10 in the AE letter to Eurand, and a summary of the DP reviewer's assessment of the adequacy of the Applicant's response is presented below.

(1) Process validation: The Applicant was requested to provide a summary of the process validation program. The response is adequate as the validation data support the Applicant's claim that production of the drug product at commercial scale is validated.

(2) Enteric coating: (b) (4) Thus, concerns regarding this coating have been adequately addressed.

(3) Stability data: The Applicant has submitted stability data to support the proposed expiry of 30 months. Thus, the response is adequate.

(4) Storage conditions: Data was submitted to support temperature excursions that may occur during transport and storage. The Applicant's proposed labeling language was deemed acceptable by the DP reviewer: "Exposure of the product to excessive heat should be avoided. Brief exposure to temperatures up to 35°C (95°F) does not adversely affect the product."

(5) Drug substance: The Nordmark DMF contained deficiencies; a separate letter was sent to Nordmark. This is discussed in the Viral DS Issues and Non-Viral DS Issues sections above.

(6) Olive oil qualification: The Applicant was requested to provide information to evaluate qualification results for olive oil testing, and to establish specifications for critical olive oil components. This was adequately addressed.

(7) Drug product acceptance criteria: A PMC is recommended. The DP reviewer determined that one part of this item was not adequately addressed, but did not preclude approval since it could be addressed as a PMC: (a) The DP reviewer noted that acceptance criteria for protease and amylase activity have been tightened slightly, but should be further adjusted and tightened as part of a PMC. The DP reviewer

determined that the remaining parts of this item were adequately addressed: (b) specifications for drug product peaks in the RP-HPLC assay; (c) release specification for phthalic acid for each of the dosage strength formulations; (d) acceptance criteria for determining content uniformity; and (e) specification for water content in the product.

(8) RP-HPLC assay validation: The Applicant has adequately addressed the concern that material might be excessively retained on the column.

(9) Qualification of the reference standard: The DP reviewer determined that the reference standard has an appropriate qualification program, and is manufactured by a process identical to that of the commercial product; thus, this request has been adequately addressed.

(10) USP lipase reference standard used: A particular batch had two different lipase specific activities depending on the reference standard used; the Applicant was requested to develop and implement a method to ensure accurate and consistent lipase activity for the reference standard. The DP reviewer determined that Eurand has adequately responded to this request. The DP reviewer noted that at the present time an assay to more accurately determine lipase activity is being developed, and acknowledged that to develop this assay will require more time and is a challenge faced by the entire pancrelipase industry.

3.3 Final Recommendation

An Approval Action is the final recommendation by CMC.

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

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

The DP 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. The PMC's concern the drug substance label, improving viral detection assays and surveillance strategies during manufacturing of the drug substance, and tightening acceptance criteria for the drug product amylase and protease potency assays. (See Section 13.6 Postmarketing Commitments of this review.)

4. Nonclinical Pharmacology/Toxicology

4.1 Initial Review Cycle

Nonclinical pharmacology/toxicology data were reviewed by the Nonclinical Pharmacology/Toxicology reviewer, Ke Zhang, and summarized in the CDTL review by Anne Pariser. (Please refer to each of those reviews for more information.)

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance[6], 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 Zenpep clinical development program. However, toxicology studies are needed if the excipients in the Zenpep 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 Zenpep 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 Zenpep.

Dr. Zhang notes that the Applicant also submitted an IND (70,563) with Zenpep on November 11, 2005, and based on the pharmacology review of this IND, all excipients in the clinical formulation of Zenpep are present in FDA-approved oral drug products. The estimated daily intake of these excipients is less than the amounts present in the FDA-approved products except for three excipients: hypromellose phthalate (b) (4) , triethyl citrate (b) (4) and hypromellose (b) (4) if 25 capsules are consumed daily. These excipients are present in higher amounts than the allowable levels in the FDA-approved products for a single-dose, which are hypromellose phthalate 302 mg, triethyl citrate 20 mg, and hypromellose 480 mg.

The Applicant did not provide the maximum daily allowable levels for these excipients in the original NDA submission. The Division requested in the 74-day letter to the Applicant (in the initial review cycle) that the maximum daily allowable levels in the FDA-approved products for hypromellose phthalate, triethyl citrate, and hypromellose be provided, and that the Applicant justify the safety of these excipients by published literature or by supporting toxicology studies. The requested information was provided, and was deemed acceptable by Dr. Zhang (see Appendix 4).

Dr. Zhang's overall conclusion from the non-clinical review of the information submitted in the NDA was that approval of the Zenpep NDA is recommended. Dr. Zhang additionally recommended that the proposed labeling be revised to include the following:

- Wording in the Pregnancy section be revised to: Category C. "Animal reproduction studies have not been conducted with Zentase. It is not known whether Zentase capsules

[6] U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf> April 2006.

can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zentase capsules should be given to a pregnant woman only if clearly needed."

- In the Carcinogenesis, Mutagenesis and Impairment of Fertility section, the paragraph referring to (b) (4) should be removed.

Since Zenpep was not recommended for Approval during the initial review cycle, the proposed labeling changes above were not negotiated with the Applicant.

4.2 Current Review Cycle

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

The recommendations for labeling revisions from the previous 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.

4.3 Final Recommendation

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

5. Clinical Pharmacology/Biopharmaceutics

5.1 Initial Review Cycle

Clinical pharmacology data were reviewed by the Clinical Pharmacology reviewer, Tien-Mien Chen, and summarized in the CDTL review by Anne Pariser. (Please refer to each of those reviews for more information.)

The studies reviewed by Dr. Chen and his conclusions are described below:

- *In vivo* intubation study (PR-001; BA study): This was a randomized open-label single-treatment crossover study that evaluated the bioavailability of Zenpep in patients with chronic pancreatitis (CP) and EPI in gastric and duodenal aspirates under fed conditions. A single fixed dose of 75,000 USP lipase units (about 1,100 U/kg) was administered. The study was not deemed to be acceptable due to questions about the reliability of the data, unclear methodology for total lipase recovery from duodenal aspirations, small size of the study and high variability of the results, enrollment of patients with high baseline lipase levels, and the lack of a specific assay method for exogenous pancreatic lipase.
- *In vitro* stability study (Stability study): This study was performed to evaluate the influence of the contact of different common types of baby foods on "gastroresistance" of Zenpep capsules. The study was conducted using the contents of 5,000 U capsules, since this strength is specifically intended for administration to infants and young children, and is likely to be administered after mixing in soft foods. The results from this study showed

acceptable stability data for Zenpep content when mixed with ten types of food (pH<5.0) for 60 minutes, such as commercial preparations of applesauce, bananas, pears, pudding, or yogurt. It was noted that the *in vitro* stability data for two of the three batches of Zenpep capsules provided in this NDA were identical, and it was not clear if there were errors in the dataset. An information request for clarification sent to the Applicant had not been responded to by the end of the review cycle.

Dr. Chen stated that the concern with the *in vitro* stability data is an Approvability issue and was included as Item #11 in the Approvable Letter (see Appendix 3). The other comments regarding the BA study were not deemed to be Approvability issues, and could be conveyed to the Applicant in a separate letter.

5.2 Current Review Cycle

The reader is referred to the Clinical Pharmacology Review by Tien-Mien Chen dated August 17, 2009, for complete information.

The studies reviewed by Dr. Chen and his conclusions are described below:

- *In vivo* intubation study (PR-001; BA study): After the submission of the original NDA on 12/14/07, the sponsor continued to enroll patients to study PR-001. The amended study report was submitted on 01/09/09, which included a total of 11 evaluable patients as judged by the sponsor. However, two of the 11 patients had negative values in the recovery of lipase due to high endogenous lipase levels and should have been excluded and another two patients had low duodenal pH (<4.0) during the food only study period which might impact the results. Furthermore, it is uncertain that the same endogenous lipase levels would occur in the two treatment periods (Ensure Plus with and without Zenpep), raising the question whether Ensure Plus only can serve as a reliable control for estimation of Zenpep bioavailability. Therefore, the study results cannot be properly interpreted. However, as stated before, the bioavailability study is not a required study for the NDA approval.
- *In vitro* stability study (Stability study): The Applicant has corrected the errors and has adequately addressed Item #11 in the Approvable Letter.

5.3 Final Recommendation

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

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

7.1 Initial Review Cycle

The reader is referred to the CDTL Review by Anne Pariser dated June 16, 2008, the Clinical Review by Marjorie Dannis dated June 15, 2008, and the Statistical Review by Freda Cooner dated June 9, 2008, for complete information.

The Applicant conducted a single pivotal study (EUR-1008-M) that demonstrated improvement in fat absorption with Zenpep treatment over placebo. In addition, the Applicant conducted a supportive study (EUR-1009-M). See table below.

Table 3. Pivotal Study and Supportive Study

Study	Study No.	No. Sites	No. Pts Enrolled	Design	Primary Endpoint
Pivotal Study	EUR-1008-M	12	34	Randomized, multicenter, double-blind, placebo-controlled, 2-treatment, crossover study	To compare the % coefficient of fat absorption* (%CFA) during oral administration of Zenpep or placebo in CF patients with EPI, ages seven to adult
Supportive Study	EUR-1009-M	10	19	Multicenter, non-randomized, open-label, multiple-dose, single-treatment study	To compare the responder rate and fecal fat excretion in CF patients with EPI before (while on prior PEP) and after administration of Zenpep in CF patients with EPI, ages one to six years

* %CFA= {[Fat intake (g/day) – Fat excretion (g/day)] / Fat intake (g/day)} X 100
* %CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet
Table above is modified form Page 15 of Clinical Review by Marjorie Dannis.

In the pivotal study (EUR-1008-M), 34 patients ages seven to 23 years (mean age 15.5 years) were randomized to receive Zenpep or matching placebo for six to seven days of treatment, followed by crossover to the alternate treatment for an additional six to seven days. The mean dose during the controlled treatment periods ranged from a mean dose of 3,900 lipase units per kilogram per day to 5,700 lipase units per kilogram per day. The mean CFA for patients during placebo treatment was 63%, and during Zenpep treatment was 88%. The mean difference in CFA on Zenpep as compared to placebo was 25%, which was a statistically significant difference ($p<0.001$; 95% CI [-32,-19]). See table below.

Table 4. ANOVA Model Results of CFA (%) [Study EUR-1008-M]

	Zenpep (N=32)	Placebo (N=31)
Mean (SEM)	88.3 (1.4)	62.7 (3.4)
SD	7.9	19.1
Median	89.8	65.8
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.3 (2.6)	62.8 (2.66)
Difference between Zenpep and Placebo		-25.5
95% CI		(-31.7, -19.3)
p value		<0.001

Table above is modified from Page 25 of the CDTL Review by Anne Pariser.

In the supportive study (EUR-1009-M), 19 patients, ages 1.2 to 6.4 years (mean age 3.9 years) were transitioned to Zenpep from their usual PEP treatment without a wash-out period. After a 4-14 days screening period on the current PEP, patients received Zenpep at individually titrated doses ranging between 2,300 and 10,000 lipase units per kg body weight per day, with a mean of approximately 5,000 lipase units per kg body weight per day for 14 days. The results show that for the cut-point of fecal fat <30% selected by the Applicant as defining patients without steatorrhea, at Screening 14 of 19 patients had a fecal fat <30%, at Visit 3 13 of 19 patients had a fecal fat <30%, and at End-of-Study 13 of 18 patients had a fecal fat <30%, and throughout the study, 16 of 19 patients had a fecal fat <30% at one or more study visits. Thus, the majority of patients were without steatorrhea during the study, whether on their usual PEP treatment or after transition to treatment with Zenpep.

There is no previous clinical experience with the formulation of Zenpep that was studied in the pivotal and supportive studies; however, there is considerable clinical experience with similar formulations of porcine-derived PEPs.

7.2 Current Review Cycle

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

7.3 Final Recommendation

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

8. Safety

The reader is referred to the CDTL Review by Anne Pariser dated June 16, 2008, the Clinical Review by Marjorie Dannis dated June 15, 2008, and the Clinical Review of Safety Update by Marjorie Dannis, dated August 12, 2009 for complete information.

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

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

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

- Fibrosing Colonopathy: FC is a rare but serious condition that may result in colonic stricture. Most of the cases of FC have been reported in younger children with CF. Although the etiology of FC is not known with certainty, FC has been associated with high dose exposure to PEPs. Consensus guidelines have been established by the Cystic Fibrosis Foundation (CFF) in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[7,8,9] (See also Appendix 1.) Continued monitoring for fibrosing colonopathy that is associated with PEP use is likely to best be performed through global safety surveillance.

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

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to aborption 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

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

testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[10,11] (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 Initial Review Cycle

The reader is referred to the CDTL Review by Anne Pariser dated June 16, 2008, and the Clinical Review by Marjorie Dannis dated June 15, 2008, for complete information.

In the initial review cycle (which included data from the 120-day safety update to March 30, 2008), the AE profile of Zenpep as described in the individual studies was consistent with the currently described AE profile of PEPs in the medical literature. In general, AEs tended to reflect underlying disease, and were most commonly reported in the gastrointestinal (GI) and respiratory systems. There were no new or noteworthy AEs noted during the initial cycle of safety review.

8.2 Current Review Cycle

The reader is referred to the Clinical Review of Safety Update by Marjorie Dannis, dated August 12, 2009 for complete information.

The safety update (to March 30, 2008) had already been reviewed in the previous review cycle.

During the current review cycle, information became available that the Applicant was continuing to market a pancrelipase product "in association with IND 70,563 and NDA 22-210." Complete safety information was required to be submitted for the unbranded pancrelipase product; this was received on June 15, 2009.

Dr. Dannis concluded in the Safety Update Review that the limited safety information submitted appears to be consistent with the known adverse event profile of PEPs. Dr. Dannis notes that the total US sales of the unbranded pancrelipase product during the reporting period (January 1, 1999 through June 1, 2009) was almost (b) (4) capsules; patient exposure to the unbranded pancrelipase product was estimated to be between approximately 911,000 and 2,250,000 patient treatment-months. Overall, 15 case reports of adverse events were received; 2 of these reports were serious spontaneous reports (one hospitalization and one pancreatic growth), while 13 of the case reports were non-serious (predominantly gastrointestinal signs and symptoms and/or lack of efficacy) spontaneous reports. The most frequently reported adverse events were lack of efficacy (8), followed by diarrhea (4) and flatulence (2). The remaining cited adverse events were single occurrences.

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

8.3 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) on May 6, 2009; there were also additional clarifications and discussion with the Division subsequent to the meeting. The committee recommended the following with the corresponding rationale:

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

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

It should be noted that the deferral for patients age > 1 month to 12 months does not require additional studies; rather, the deferral for this age category is for the development of an age-appropriate formulation (i.e., a capsule containing 2,000 to 4,000 lipase units). Such a formulation will allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

In addition, it should be noted that published literature data with PEPs in general, not data with the particular formulation (i.e., Zenpep) 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., Zenpep) comes from the randomized double-blind placebo-controlled

cross-over study using that formulation (i.e., EUR-1008-M) 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, EUR-1008-M can be considered to be a "bridging study" to the existing body of evidence from the literature for a range of pancreatic enzyme formulations.

The above recommendations are generally consistent with those for Creon. In particular, the approval letter for Creon reflects a waiver for patients ages 0 to 1 month, and a deferral for patients age > 1 month to 12 months (for the purpose of the development of an age-appropriate formulation); it also includes a statement that no additional pediatric studies are needed.

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. Zenpep is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

Initial Review Cycle

In the initial review cycle, site inspections of two clinical sites and the central laboratory were performed by the Division of Scientific Investigations (DSI) as part of the review of this NDA submission. The sites inspected were part of the pivotal study EUR-1008-M. That information is provided in the Clinical Inspection Summary memorandum by Khairy Malek, M.D., and summarized in the CDTL review by Anne Pariser (see each of those documents for more detailed information). The site inspections are summarized in the table below.

Table 5. Overview of two sites inspected (Study EUR-1008-M)

Site No.	Investigator / Location	No. patients enrolled	Primary Endpoint Results
Site 105	Steven Boas, M.D., Glenview, IL	Six	Not available at clinical site (obtained at Mayo Central Laboratory*)
Site 103	David Schaeffer, M.D., Jacksonville, FL	Four	Not available at clinical site (obtained at Mayo Central Laboratory*)

* Inspection of the lab was limited to comparing the lab results for the primary endpoint obtained at the two clinical sites (103 and 105) with the data reported to the FDA.

Information in the table above is taken from the CTDL review by Anne Pariser.

Review of the data showed that the data in the lab records were the same as the data reported to the FDA. The overall assessment of the inspector from the inspection of the two clinical sites and the Mayo Central Laboratory was that the data are reliable and can be used in support of the NDA.

Current Review Cycle

No additional site inspections were requested in the current review cycle.

11.3 Drug Shortage

Currently, Creon is the only PEP that is available on the market that has undergone the NDA review process. There are other PEPs on the market that have not undergone the NDA review process, but these will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010. Thus, the approval of Zenpep may help to prevent a drug shortage from developing in the near future (i.e., by April 28, 2010; the time that all marketed PEPs must have an approved NDA).

12. Labeling

12.1 Proprietary name

Initial Review Cycle:

In the initial review cycle, the name "Zentase" was submitted. A review of the trade name "Zentase" was performed by Deveonne Hamilton-Stokes in the Division of Medication Errors Prevention (DMEP), Office of Surveillance and Epidemiology (OSE); that review is summarized in the CDTL review by Anne Pariser. Please see each of those reviews for more detailed information.

DMEP considered the proposed trade name "Zentase" unacceptable (under 21 CFR 201.10(c)(5)) based on the orthographic similarity of the name and potential for confusion with two other marketed products Pentasa and Zantac.

A letter was sent to the Applicant during the review cycle (dated March 28, 2008) notifying the Applicant that the proposed trade name "Zentase" was unacceptable and requesting submission of two alternative trade names. The Applicant subsequently proposed two new names "ZenPep" and "Zenase;" the review of those names was still under review at the time of writing of the CDTL Review of the previous review cycle by Anne Pariser.

Current Review Cycle:

In the current review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of "Zenpep" was acceptable. Please see DMEPA Proprietary Name Reviews (dated March 6, 2009 and July 30, 2009) by Deveonne Hamilton-Stokes for complete information.

In the March 6, 2009 Proprietary Name Review, the reviewer concluded that based on the Proprietary Name Risk Assessment findings, the proposed name, Zenpep, is not vulnerable to name confusion that could lead to medication errors.

In the July 30, 2009 Proprietary Name Review, the reviewer conducted a re-assessment of the proprietary name in response to a notification that NDA 22-210 may be approved within 90 days. The reviewer noted that since the March 6, 2009 review, none of Zenpep's product characteristics have changed. The reviewer added that during this re-review one new name (Zipsor) was identified for its similarity to Zenpep. The reviewer concluded that the results of the Failure Mode Effects Analysis found that the proposed name, Zenpep, is not vulnerable to name confusion that could lead to medication errors with Zipsor.

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

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the name acceptable from a promotional perspective; an e-mail stating this was sent from Nina Ton, Safety Regulatory Project Manager OSE/DDMAC on February 17, 2009. This is also documented in the Tradename review by Deveonne Hamilton-Stokes dated July 30, 2009.

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 drug in the class that was recently approved, Creon.

In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMEPA Labeling Review, the DRISK Proposed REMS Review, the DRISK Patient Labeling and Medication Guide Review, the DTP Carton and Container Label Review, the DDMAC Labeling Review, and the SEALD Labeling Review. The reader is referred to each of these reviews for complete information.

The most notable revisions are summarized below:

Physician Labeling:

- Administration (Section 2.2 of Label): A statement that capsule contents may be sprinkled on small amounts of acidic soft food with a pH of ≤ 4.5 was included in this section based on the results of the *in vitro* study. Commercially available preparations of bananas, pears, and applesauce were stated as examples of foods that had a pH of ≤ 4.5 because these particular foods were studied in the *in vitro* study, and these foods from different manufacturers were consistently shown to have the pH stated.

- Adverse Reactions – Clinical Trials Experience (Section 6.1 of Label): A description of the adverse reactions in the open-label single-arm study (Study EUR-1009M) which included patients between the age of 1 and 6 years was included in addition to the summary of adverse reactions in the double-blind placebo-controlled trial (EUR-1008M) which included patients between the age of 7 and 23 years.

- Use in Specific Populations – Pediatric Use (Section 8.4 of Label): A brief description of the results of the open-label single-arm study (Study EUR-1009M) which included patients between the age of 1 and 6 years was included (b) (4)

- Overdosage (Section 10 of Label): Information about one 10-year old patient who was administered a dose of greater than 10,000 lipase units/kg/day was included.

- Clinical Studies (Section 14 of Label): The results of EUR-1009M which included patients between the age of 1 and 6 years were included in addition to the results of the double-blind placebo-controlled trial (EUR-1008M) which included patients between the age of 7 and 23 years.

- How Supplied/Storage and Handling (Section 16 of Label): The DP reviewer revised Section 16 based on data submitted by the Applicant to support temperature excursions that may occur during transport and storage. The following is stated in this section of the label:

  ”Avoid excessive heat. Store at room temperature (68-77°F; 20-25°C), brief excursions permitted to 15-40°C (59-104°F).”

Medication Guide:

- Giving ZENPEP to infants: In order to communicate in more patient-friendly language the statement in the Administration section (Section 2.2 of the label) about foods that the contents of the capsules may be sprinkled on (i.e., small amounts of acidic soft food with a pH of ≤ 4.5 such as commercially available preparations of bananas, pears, and applesauce), the following is stated in this section of the Medication Guide:

  “Open the capsules and sprinkle the contents on a small amount of applesauce, pureed bananas or pears. These foods should be the kind found in baby food jars that you buy at the store, or other food recommended by your doctor.”

Carton and Container Labeling:

- Unit of Use: The capsules are packaged in bottles containing 100 capsules or 500 capsules; each bottle contains one desiccant. Because of the concern that capsules may be dispensed without a desiccant, the carton and container labeling was revised to indicate that the container is a unit of use container; the statement “Pharmacist: Dispense in original container” was added to the carton and container labeling. This is intended to communicate to the pharmacist that a specific quantity of the drug product (i.e., the 100 or 500 capsule bottle) is intended to be dispensed without further modification.

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)

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

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

The REMS element is the following:

- Medication Guide

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

The timetable for submission of assessments will be:

- 1st Assessment: (March 23, 2011) 18 months after NDA approval
- 2nd Assessment: (September 23, 2012) 3 years after NDA approval
- 3rd Assessment: (September 23, 2016) 7 years after NDA approval

A notable item of the REMS for Zenpep is the following:

Unit of Use: The REMS specifies that Zenpep is available in unit of use bottles. The capsules are packaged in bottles containing 100 capsules or 500 capsules; each bottle contains one desiccant. Because of the concern that capsules may be dispensed without a desiccant, the REMS includes a statement that the container is a unit of use container. This is intended to communicate that a specific quantity of the drug product (i.e., the 100 or 500 capsule bottle) is intended to be dispensed without further modification.

13.4 Recommendation for Postmarketing Required Pediatric Studies

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

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

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

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

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the

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

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

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

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

   The timetable you submitted on August 19, 2009 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: by July 15, 2010
   Study Completion Date: by July 1, 2022
   Final Report Submission: by December 31, 2022

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

   The timetable you submitted on August 19, 2009 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: by July 15, 2010
   Study Completion Date: by July 1, 2022
   Final Report Submission: by December 31, 2022

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

NDA 22-210 Postmarketing Commitments

(1) Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the manufacturing process. After 50 drug product lots are manufactured, specifications will be reevaluated and adjusted to reflect manufacturing history and capability.

Final Report Submission: by September 2011

DMF 7090 Postmarketing Commitments

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

Final Report Submission: by December 2010

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

Final Report Submission: by June 2011

(3) Establish lot release specifications for PPV and PCV2 for the drug substance.

Final Report Submission: by December 2009

(4) Perform additional monitoring of enveloped viral load entering the manufacturing process. The control program will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with an appropriate control strategy.

Final Report Submission: by June 2011

(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. Revise the assays, and submit assay validation data, together with acceptance criteria.

Final Report Submission: by December 2010

(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 December 2009

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

Final Report Submission: by December 2009

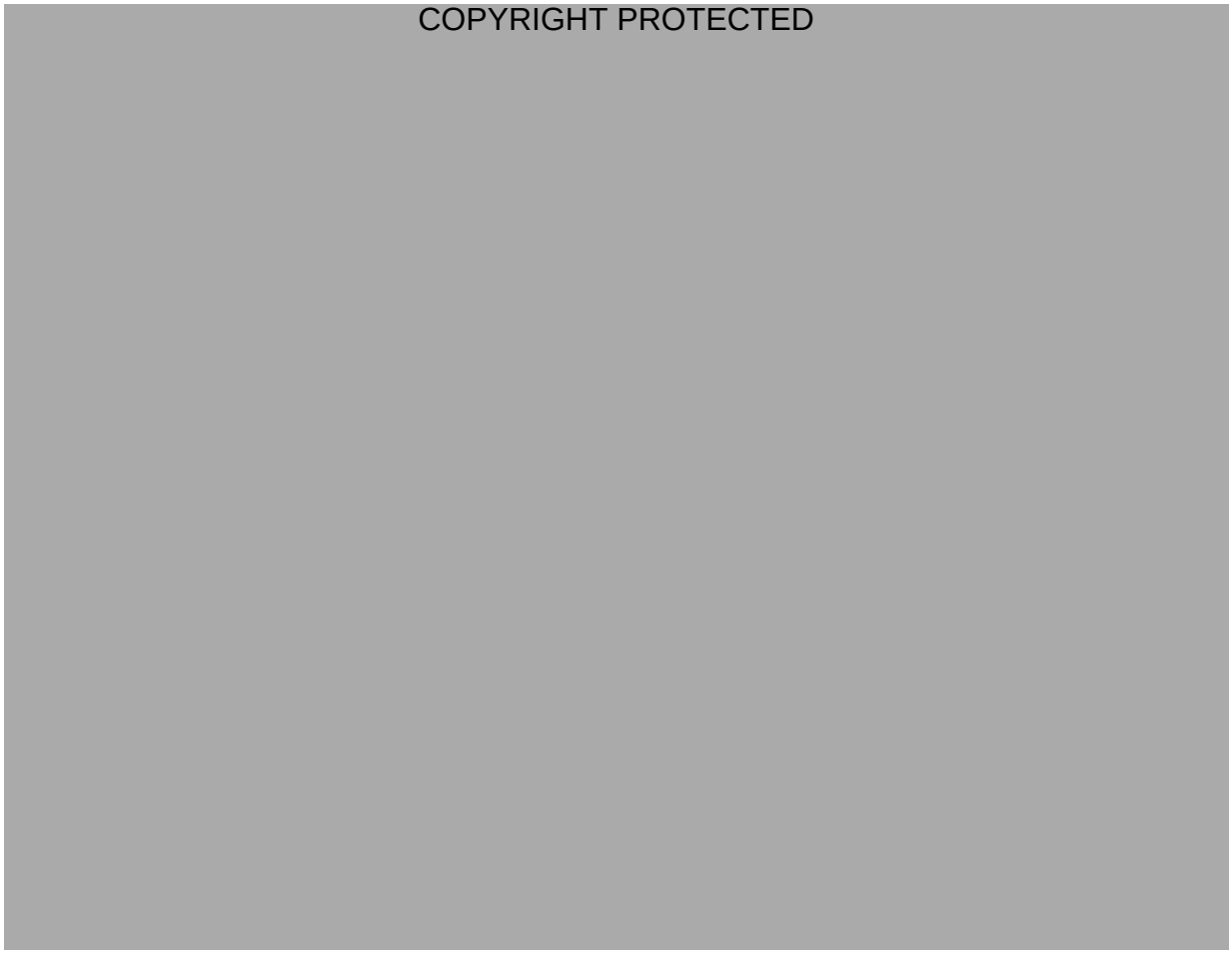
(8) Assign an expiration date to the pancrelipase drug substance label used for production of the Zenpep product. An expiration date will be included on the drug substance label by December 2009.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1

The CFF Dosing Guidelines (from Borowitz et al., 1995[12]) are provided below:



Borowitz et al. 2002[13] states:

Fitzsimmons et al. 1997[14] states:

[12] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[13] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[14] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22210	ORIG 1	EURAND PHARMACEUTICALS LTD	ZENTASE
NDA 22210	ORIG 1	EURAND PHARMACEUTICALS LTD	ZENTASE

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/s/

ANIL K RAJPAL
08/21/2009