

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-222Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	February 9, 2012
<b>From</b>	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/ BLA #</b>	NDA 22-222
<b>Applicant</b>	Aptalis Pharma US Inc.
<b>Date of Submission</b>	September 1, 2011
<b>PDUFA Goal Date</b>	March 1, 2012
<b>Proprietary Name / Established (USAN) names</b>	Ultresa® pancrelipase
<b>Dosage forms / Strength</b>	Ultresa® (pancrelipase) delayed release-capsules for oral administration, in USP units <ul style="list-style-type: none"><li>▪ Ultresa 13,800 lipase/27,600 protease/27,600 amylase</li><li>▪ Ultresa 20,700 lipase/41,400 protease/41,400 amylase</li><li>▪ Ultresa 23,000 lipase/46,000 protease/46,000 amylase</li></ul>
<b>Proposed Indication</b>	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
<b>Recommended Action:</b>	Approval under 21 CFR 314

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## 1. Introduction

A Complete Response (CR) Letter was sent by the Division on November 28, 2010. This resubmission, received September 1, 2011, is a complete response to that letter, and represents the fifth review cycle for Ultresa (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP); Ultresa is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

In each of the previous cycles (i.e., the first, second, third, and fourth review cycles), deficiencies were identified by the Chemistry, Manufacturing, and Controls (CMC) discipline.

The first review cycle CMC deficiencies in the Approvable (AE) letter were related to: (1) drug substance and drug product issues (separate letter with 22 items sent to the drug substance DMF holder [included four items related to viral issues]; separate letter with nine items sent to the drug product DMF holder); (2)(a) stability data to support 24-month expiry; (2)(b) stability data across lots; (2)(c) release and stability testing ( (b) (4) content, product-related substances, impurities); and (2)(d) USP lipase reference standard used.

The second review cycle CMC deficiencies in the CR letter were related to: (1) drug substance and drug product issues (separate letter with 23 items sent to the drug substance DMF holder [included seven items related to viral issues and two items related to microbiology issues]; separate letter with six items sent to the drug product DMF holder); (2) clarification regarding stability testing (should be performed on packaged DP not prior to packaging); (3) data collected using the updated stability program and acceptance criteria; (4) stability once final container opened (forced degradation studies); and (5) stability data for 12 count bottle to support 16-month expiry (or revision of label to state 12 month expiry).

The third review cycle CMC deficiencies in the CR letter were related to: (1) drug substance and drug product issues (two separate letters [one letter with six items related to microbiology issues, and the other letter with four items related to other drug substance issues] sent to the drug substance DMF holder; separate letter with two items sent to the drug product DMF holder); and (2) a discrepancy in the description of the capsules printing between the NDA submission and the description provided in the package insert.

The fourth review cycle CMC deficiencies in the CR letter were related to drug substance issues. The CR letter cited a letter sent to the drug substance DMF holder, and minutes of a meeting with the drug substance DMF holder and the Applicant. Facility inspection deficiencies were also included in the CR letter.

No clinical deficiencies were identified in any of the review cycles. The initial submission included results from a randomized double-blind cross-over clinical study using the To be Marketed Product (TbMP) (UMT20CF05-01; n=31; ages 8 to 37 years). The second, third, fourth, and current submissions contain clinical study safety updates; in addition, the second submission included results from an open label study using the TbMP (UMT20CF07-01; n=9; ages 7 to 11 years). The TbMP is the same formulation as the unapproved

Commercially Marketed Product (CMP) that was marketed until April 28, 2010 (the date that unapproved PEPs could no longer be marketed).

It should be noted that the Applicant name changed from Axcan Pharma US, Inc. to Aptalis Pharma US, Inc; the Division was notified of this in a letter submitted to the NDA October 13, 2011 and received October 14, 2011. It should also be noted that the drug product Drug Master File (DMF) Holder (DMF #15681) was formerly Eurand S.p.A. (in prior review cycles), and is currently Aptalis Pharma SRL.

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).<sup>1,2,3</sup>

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.<sup>1,2,3</sup> (See also Section 8 and Appendix 1.)

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<sup>1</sup> 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.

<sup>2</sup> 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.

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

## 2.2 Regulatory History

### 2.2.1 Pancreatic Enzyme Products

Approved PEPs: Four PEPs have been approved under NDA to date:

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

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

Unapproved PEPs: Unapproved PEPs can no longer be marketed effective April 28, 2010. PEPs had been available since prior to the Federal Food, Drug, and Cosmetic Act of 1938; most PEPs had been available since before Drug Efficacy Study Implementation (DESI; pre-1962).

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

**Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products**

Year	Federal Register Notices
April 1995	Notice of Final Rule: All PEPs must obtain FDA approval under NDA in order to remain on the market.
April 2004	Notice of Requirement for NDA Approval: All PEPs must obtain NDA approval within the next four years (deadline April 28, 2008)
October 2007	Notice of Extension: FDA would use enforcement discretion for the PEPs. In order to continue marketing their products, manufacturers must have: <ul style="list-style-type: none"> <li>▪ open IND by April 28, 2008,</li> <li>▪ NDA submitted by April 28, 2009, and</li> <li>▪ approved NDA by April 28, 2010.</li> </ul>

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 each of the 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 each of the sponsors of the approved PEPs – Creon (May 9, 2011), Zenpep (June 10, 2011), and Pancreaze (June 20, 2011).

## 2.2.2 Regulatory History of Ultresa

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

**Table 2. Pertinent Regulatory History of Ultresa\***

Date	Event
December 1992	Original IND submission*
May 2007	Fast Track Designation
July 2007	Modules 1 to 4 of NDA 22-222 submitted
October 2007	Module 5 of NDA 22-222 submitted
<b>July 2008</b>	<b>Approvable Action (1<sup>st</sup> action)</b>
September 2008	Meeting with the Sponsor to discuss items in the Division's Approvable Letter
April 2009	Class II Resubmission <sup>#</sup>
<b>September 2009</b>	<b>Complete Response Action (2<sup>nd</sup> action)</b>
November 2009	Class II Resubmission <sup>#</sup>
<b>May 2010</b>	<b>Complete Response Action (3<sup>rd</sup> action)</b>
May 2010	Meeting with the Sponsor to discuss items in the Division's CR Letter
May 2010	Class II Resubmission <sup>#</sup>
<b>November 2010</b>	<b>Complete Response Action (4<sup>th</sup> action)</b>
September 2011	Class II Resubmission <sup>#</sup> (current submission)
January 2012	Meetings with the Applicant and with (b) (4) to discuss methods transfer report submissions, and information needed for adequate assay transfer studies.

\*IND 41387; <sup>#</sup>Complete Response to the Action Letter

It should be noted that Ultresa was commercially available in the US from 1991 to April 2010 (see Section 2.2.1); it was marketed under the name "Ultrase." The CMP formulation that was on the market from 2003 to April 2010 and the TbMP are the same formulation.

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

- First Review Cycle:
  - Cross Discipline Team Leader Review by Anne Pariser, dated July 1, 2008
  - Clinical Review by Joanna Ku, dated July 1, 2008
  - Statistical Review by Stella Grosser, dated June 25, 2008
- Second Review Cycle:
  - Cross Discipline Team Leader Review by Anil Rajpal, dated September 9, 2009
- Third Review Cycle:
  - Cross Discipline Team Leader Review by Anil Rajpal, dated May 5, 2010
- Fourth Review Cycle:
  - Cross Discipline Team Leader Review by Anil Rajpal, dated November 24, 2010

Correspondence from previous review cycles cited by this reviewer consists of the following:

- First Review Cycle:
  - Approvable Letter sent to Axcan Pharma US, Inc. (c/o CanReg, Inc.) dated July 1, 2008
  - Deficiency Letter sent to (b) (4) dated July 1, 2008 (Master File # (b) (4))
  - Deficiency Letter sent to Eurand dated July 1, 2008 (Master File #15681)
- Second Review Cycle:
  - Complete Response Letter sent to Axcan Pharma US, Inc. (c/o CanReg, Inc.) dated September 9, 2009
  - Deficiency Letter sent to (b) (4) dated September 15, 2009 (Master File # (b) (4))
  - Deficiency Letter sent to Eurand dated September 15, 2009 (Master File #15681)
- Third Review Cycle:
  - Complete Response Letter sent to Axcan Pharma US, Inc. (c/o CanReg, Inc.) dated May 5, 2010
  - Deficiency Letter sent to (b) (4) dated May 4, 2010 (Master File # (b) (4))
  - Deficiency Letter sent to (b) (4) dated May 3, 2010 (Master File # (b) (4))
  - Deficiency Letter sent to Eurand dated May 4, 2010 (Master File #15681)
- Fourth Review Cycle:
  - Complete Response Letter sent to Axcan Pharma US, Inc. dated November 28, 2010
  - Information Request Letter sent to (b) (4) dated October 27, 2010 (Master File # (b) (4))
  - Minutes of November 15, 2010 Meeting with Axcan and (b) (4) (filed under NDA 22-222 November 24, 2010)

### 2.3 Current Submission

The NDA resubmission was received on September 1, 2011. It was classified as a six-month resubmission with a PDUFA deadline of March 1, 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 20, 2011 (NDA 22-222)
- (2) CMC Reviews from Division of Therapeutic Proteins (DTP):
  - (a) NDA Review by Richard Ledwidge dated February 1, 2012 (NDA 22-222)
  - (b) DMF Review by Richard Ledwidge dated February 1, 2012 (DMF (b) (4))
  - (c) CMC Summary Review by Emanuela Lacana dated February 9, 2012 (NDA 22-222)
- (3) Microbiology Reviews from New Drug Microbiology Staff (NDMS)
  - (a) NDA Review by Stephen Langille dated January 31, 2012 (NDA 22-222)
  - (b) DMF Review by Stephen Langille dated January 31, 2012 (DMF (b) (4))
- (4) Division of Medical Policy Programs (DMPP) Review by Sharon Mills dated February 6, 2012 (NDA 22-222)
- (5) Office of Prescription Drug Promotion (OPDP) Review by Twyla Thompson and Kathleen Klemm dated February 8, 2012 (NDA 22-222)

- (6) Reviews from the Division of Medication Error Prevention and Analysis (DMEPA):
- (a) Proprietary Name Review by Manizheh Siahpoushan dated December 6, 2011 (NDA 22-222)
  - (b) Label and Labeling Review by Manizheh Siahpoushan dated November 2, 2011 (NDA 22-222)

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

- Proprietary Name Granted Letter sent to Aptalis Pharma US, Inc. dated December 19, 2011 (signed by Carol Holquist, Director Division of Medication Error Prevention and Analysis [DMEPA])

The reviews should be consulted for more specific details of the application. The reader is also referred to the CDTL Reviews for the initial, second, third, and fourth review cycles, dated July 1, 2008, September 9, 2009, May 5, 2010, and November 24, 2010, respectively, as well as to the primary review documents from each of those cycles.

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 Reviews by Richard Ledwidge dated February 1, 2012 (NDA 22-222 and DMF (b)(4)) the CMC Secondary Review by Emanuela Lacana dated February 9, 2012 (NDA 22-222), and the Microbiology Reviews by Stephen Langille dated January 31, 2012 (NDA 22-222 and DMF (b)(4)) for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (b)(4) (b)(4) (b)(4) the drug substance Drug Master File (DMF) holder (DMF # (b)(4)) 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 (b)(4) (b)(4). The glands (b)(4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b)(4) (among others), which results in pancrelipase DS. The resulting pancrelipase DS is used for manufacture of drug product (DP).

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

(into hard gelatin capsules). Ultresa capsules come in three dosage strength formulations, containing 13,800 USP units lipase, 20,700 USP units lipase, and 23,000 USP units lipase. The capsules contain identical pancrelipase formulated minitables that are 2.0 mm in diameter. A stability study with the minitables mixed in foods (i.e., applesauce, pudding, and yogurt) was conducted to support the use of various foods to administer the minitables (see Section 5 Clinical Pharmacology).

Overview of Final Product Release and Packaging: The final DP release includes assessments of release specifications such as lipase activity, impurities testing, and stability data. The final packaging is into high-density polyethylene (HDPE) bottles (containing 100 capsules or 500 capsules) for commercial distribution. Each bottle contains a desiccant package.

### 3.1 Initial Review Cycle

In the initial review cycle, the Drug Substance, Drug Product, and Final Product Release and Packaging reviews were conducted by Wei Guo, 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, Drug Product, Final Product Release and Packaging, and Virology reviews; an Approval (AP) action was recommended from the Microbiology Review.

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

#### 3.1.1 DS Viral Issues (first cycle)

The key assessments of the virology reviewer were that the viral inactivation studies and clearance studies were not adequate.

- Viral inactivation studies: Although the evaluation of viral inactivation showed results consistent with those of other DS manufacturers (i.e., two to three log inactivation of enveloped viruses and the non-enveloped virus Reo3, but no such inactivation of PPV), the evaluation of viral inactivation was conducted only after one of the steps of the manufacturing process (the (b) (4) step; after (b) (4)). In response to DTP's request, (u) (4) initiated an evaluation of the (b) (4) steps, but results of those evaluations were not available at the time of the previous review.
- Viral clearance studies: The model viruses selected for assessment of viral clearance were not adequate as representative models for HEV and EMCV were not included. In

response to DTP's request, (b) (4) added FCV (model for HEV) and EMCF, and this was deemed suitable for validation of the manufacturing process for viral clearance. However, given the large amounts of PPV, PCV1, and PCV2 associated with the tissue source, it was thought that there may also be other viruses present; thus, Q-PCR testing for selected non-enveloped viruses (including HEV, EMCV, SVDV, Reo, Rota A, Influenza A, and VSV) was recommended. The virology reviewer noted that Q-PCR testing would not provide information on whether live viruses are present, so infectivity testing for batches positive by the above Q-PCR tests, and routine PPV, PCV1, and PCV2 infectivity testing were also recommended.

Deficiency items for viral issues that were sent to (b) (4) were related to (see final wording of Items #1 to #4 in Deficiency Letter to (b) (4) [Control of Adventitious Viral Agents section] in Appendix 2): (1) risk mitigation for adventitious agents; (2) viral inactivation studies; (3) validation of viral infectivity assays; and (4) specifications for adventitious agents (including Q-PCR and infectivity testing).

### 3.1.2 DS Non-Viral Issues (first cycle)

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) and (b) (4)) was performed. Detailed descriptions and validation reports for the analytical methods and enzyme assays used also were provided. The DS reviewer noted that the drug substance used in NDA 22-222 is DS 1286, a (b) (4) (b) (4) DS 1208 (a primary drug substance). 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 (b) (4) were related to (see final wording of Items #1 to #19 in Deficiency Letter to (b) (4) [CMC for Drug Substance section] in Appendix 2): (1) amount of raw material used and limits on process-related impurities; (2) acceptance criteria (lipase, amylase, protease, (b) (4) content, microbial limits), storage conditions, and expiration date; (3) process data for DS 1208 (a primary drug substance) and DS 1286 ((b) (4)); (4) rejected batches may not be reworked or reprocessed; (5) in-process lipase activity and microbial limits acceptance criteria; (6) (b) (4) characterization study; (7) DS characterization for amylase; (8) DS 1286 release testing; (9) specification for (b) (4) content and impurities for release testing; (10) tightening of protease and amylase activity acceptance criteria; (11) (b) (4) specification for DS release; (12) olive oil qualification; (13) linearity of assays (lipase, amylase, and protease); (14) demonstration of predicted activity (lipase, amylase, and protease); (15) validation of assays (lipase, amylase, and protease); (16) trend of stability data for DS 1208 and DS 1286; (17) expiry for DS 1208; (18) expiry for DS 1286; and (19) DS release test sampling plan.

### 3.1.3 DP Issues (first cycle)

The overall findings of the DP reviewer were that there were a number of deficiencies identified for the manufacture of DP.

DP deficiencies in the Deficiency Letter to Eurand were related to (see final Deficiency Letter to Eurand wording in Appendix 3): (1) release and acceptance criteria; (2) stability data; (3) internal reference standards that reflect the DP commercial manufacturing process; (4) development and implementation of an internal working lipase reference standard; (5) qualification for the lipase olive oil substrate; (6) (b) (4) assay method used in the (b) (4) step of manufacturing; (7) description of the (b) (4) process for the (b) (4) step of manufacturing; (8) information regarding the CMC for hypromellose phthalate used for the enteric coating of the minitables; and (9) summary of the process validation program.

### **3.1.4 Final Product Release and Packaging Issues (first cycle)**

The overall findings of the Final Product Release and Packaging reviewer were that there were a number of deficiencies identified for the final product release and packaging.

Final product release and packaging deficiencies in the CR Letter to Axcan Pharma US, Inc. were related to (see final CR Letter to Axcan Pharma US, Inc. wording in Appendix 4): (1) drug substance and drug product (separate letter with 22 items sent to the drug substance DMF holder [included four items related to viral issues]; separate letter with nine items sent to the drug product DMF holder); (2a) stability data to support 24-month expiry; (2b) stability data across lots; (2c) release and stability testing ((b) (4) content, product-related substances, impurities); and (2d) USP lipase reference standard used.

## **3.2 Second Review Cycle**

In the second review cycle, the reviews of Drug Product, Drug Substance Non-Viral Issues, and Final Product Release and Packaging were conducted by Wei Guo, the review of Drug Substance Viral Issues was conducted by Howard Anderson, and the review of Microbiology was conducted by Stephen Langille. 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.)

### **3.2.1 DS Viral Issues (second cycle)**

The overall findings of the DS Viral Issues reviewer in the second review cycle were that although many of the deficiencies identified in the first cycle were adequately addressed, there were a number of deficiencies that still existed and that precluded approval.

Deficiency items for DS viral issues that were sent to (b) (4) were related to (see final wording of Items #15 to #21 in Deficiency Letter to (b) (4) in Appendix 5): (15) sanitizing procedures to prevent cross contamination between DS batches; (16) development and validation of PCV1 infectivity assay; (17) lot release specifications for PPV and PCV2; (18) estimate of viruses per dose of DS, and proposal for appropriate control; (19) plans for improvement of sensitivity of qPCR assays for selected viruses; (20) risk assessment and control strategy for hokovirus; and (21) risk mitigation plan for new and emerging adventitious agents.

### 3.2.2 DS Non-Viral Issues (second cycle)

The overall findings of the DS Non-Viral Issues reviewer in the second review cycle were that although many of the deficiencies identified in the first cycle were adequately addressed, there were a number of deficiencies that still existed and that precluded approval.

Deficiency items for non-viral DS issues that were sent to (b) (4) were related to (see final wording of Items #1 to #14 in Deficiency Letter to (b) (4) in Appendix 5): (1) RP-HPLC assay methods to monitor purity of DS 1286; (2) RP-HPLC identity assay acceptance criteria; (3) validation of (b) (4) process of DS 1208; (4) target lipase activity for glands used in manufacture of DS 1208; (5) RP-HPLC assay used in release and stability testing; (6) sample DS label; (7) forced degradation studies to evaluate suitability of RP-HPLC assay for stability testing; (8) clarification of term “finished product” in report; (9) acceptance criteria for release testing of DS 1208; (10) olive oil testing program; (11) enzyme assay method validation reports; (12) expiry for DS 1208; (13) method to ensure accurate and consistent lipase activity for the working reference standard; and (14) lipase activity results using (b) (4)

### 3.2.3 DP Issues (second cycle)

The overall findings of the DP reviewer in the second review cycle were that although many of the deficiencies identified in the first cycle were adequately addressed, there were a number of deficiencies that still existed and that precluded approval.

Deficiency items for DP issues that were sent to Eurand were related to (see final wording of Items #1 to #6 in Deficiency Letter to Eurand in Appendix 6): (1) release testing data; (2) microbial limit testing results per lot; (3) release test sampling methods; (4) release and stability acceptance criteria for the RP-HPLC assay; (5) acceptance criteria for moisture content; and (6) data collected using the updated stability program and acceptance criteria.

### 3.2.4 Final Product Release and Packaging Issues (second cycle)

The overall findings of the Final Product Release and Packaging reviewer in the second review cycle were that although many of the deficiencies identified in the first cycle were adequately addressed, there were a number of deficiencies that still existed and that precluded approval.

Deficiency items for final product release and packaging issues that were sent to Axcan Pharma US, Inc. were related to (see final wording of Items #1 to #5 in CR Letter to Axcan Pharma US, Inc. in Appendix 7): (1) drug substance and drug product (separate letter with 23 items sent to the drug substance DMF holder [included 7 items related to viral issues and 2 items related to microbiology issues]); (2) clarification regarding stability testing (should be performed on packaged DP not prior to packaging); (3) data collected using the updated stability program and acceptance criteria; (4) stability once final container opened (forced degradation studies); and (5) stability data to support 16-month expiry.

### 3.2.5 Microbiology Issues (second cycle)

DMF (b) (4) was reviewed in the second cycle by the Microbiology Reviewer as a result of a facility inspection that revealed abnormally high counts of spore forming bacteria in the drug substance. The Microbiology Reviewer reviewed the DS manufacturing process for flaws that could lead to increased numbers of anaerobic microorganisms.

The Microbiology Reviewer concluded in the second review cycle that DMF (b) (4) is adequate to support NDA 22-222; however, he recommended that (b) (4) provide information on selected manufacturing processes. These items were included in the letter sent to (b) (4) and were related to (see final wording of Items #22 and #23 in Deficiency Letter to (b) (4) in Appendix 5): (22) washing, processing, and microbiological acceptance criteria for pancreas glands; and (23) information about manufacturing process (including storage time, temperature, and data showing effect of storage on microbial growth).

### 3.2.6 Facility Inspections and Consult with DAIOP (second cycle)

Eurand Inspection: A facility inspection of Eurand took place in June 2008. Deficiencies were not noted by the field investigator.

(b) (4) Inspection: A facility inspection of (b) (4) was conducted in (b) (4), and a FDA Form 483 with (b) (4) observations was issued.

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 conclusions of Dr. Benjamin Lorenz (see Consult Review dated June 5, 2009) 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.

### **3.3 Third Review Cycle**

In the third review cycle, the reviews of Drug Product, Non-Viral Drug Substance Issues, and Final Product Release and Packaging were conducted by Wei Guo, the review of Viral Drug Substance Issues was conducted by Howard Anderson, and the review of Microbiology was conducted by Stephen Langille. 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.)

#### **3.3.1 DS Viral Issues (third cycle)**

The overall findings of the DS Viral Issues reviewer in the third review cycle were that deficiencies exist, but these do not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's). (See Sections 3.5.1 and 13.6 of this CDTL review.)

#### **3.3.2 DS Non-Viral Issues (third cycle)**

The overall findings of the DS Non-Viral Issues reviewer in the third review cycle were that although the majority of the deficiencies identified in the second cycle were adequately addressed, there were some deficiencies that still existed and that precluded approval.

Deficiency items for non-viral DS issues that were sent to (b) (4) were related to (see final wording of Items #1 to #4 in Deficiency Letter to (b) (4) in Appendix 8): (1) RP-HPLC assay acceptance criteria in release and stability protocols; (2) real time stability data to support a 24-month expiry for the 1208 DS; (3) clarification of testing site(s) for performance of release assays; and (4) stability data to support the proposed shelf-life.

#### **3.3.3 DP Issues (third cycle)**

The overall findings of the DP reviewer in the third review cycle were that although the majority of the deficiencies identified in the second cycle were adequately addressed, there were two deficiencies that still existed and that precluded approval.

Deficiency items for DP issues that were sent to Eurand were related to (see final wording of Items #1 and #2 in Deficiency Letter to Eurand in Appendix 9): (1) revised RP-HPLC assay acceptance criteria to reflect manufacturing history and process capability; and (2) additional stability data to support the proposed shelf life.

#### **3.3.4 Final Product Release and Packaging Issues (third cycle)**

The overall findings of the Final Product Release and Packaging reviewer in the third review cycle were that deficiencies identified in the second cycle were adequately addressed, but an additional deficiency item was identified (during the course of the third review cycle) that precluded approval.

Deficiency items for final product release and packaging issues that were sent to Axcan Pharma were related to (see final wording of Items #1 and #2 in CR Letter to Axcan Pharma in Appendix 10): (1) DS and DP issues (two separate letters [one letter with six items related to microbiology issues, and the other letter with four items related to other DS issues] sent to the DS DMF holder; separate letter with two items sent to the DP DMF holder); and (2) a discrepancy in the description of the capsules printing between the NDA submission and the description provided in the package insert.

### 3.3.5 Microbiology Issues (third cycle)

The overall findings of the Microbiology reviewer in the third review cycle were that there were a number of deficiencies identified that precluded approval. DMF (b) (4) was reviewed in the third cycle by the Microbiology Reviewer because of testing done by the FDA's Southwest Regional Lab showing that one of seven drug substance samples obtained from (b) (4) was positive for *Bacillus cereus* enterotoxin; the Microbiology Reviewer also assessed the adequacy of (b) (4) response to items that were identified in the second review cycle.

Deficiency items for DS microbiology issues that were sent to (b) (4) were related to (see final wording of Items #1 through #6 in the Deficiency Letter to (b) (4) in Appendix 11): (1) justification for in-process holding times (especially prior to (b) (4)); (2) in-process total aerobic microbial count (TAMC) alert and action levels (for 1206 and 1208); (3) explanation for wide range of TAMC prior to (b) (4) (for 1206 lots) and corrective actions; (4) rationale for selection of (b) (4) processes (b) (4); (5) request to provide the maximum storage time for the 1208 (b) (4) and (6) commitment to test *Bacillus cereus* enterotoxin prior to release including description of methods and validation.

### 3.3.6 Facility Inspections and Health Hazard Evaluation (third cycle)

Eurand Inspection: Based on the Establishment Evaluation System (EES) report, there is an "Acceptable" recommendation for Eurand dated August 19, 2008.

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation for (b) (4) dated August 4, 2009.

Health Hazard Evaluation (HHE): A HHE Review was conducted by Anil Rajpal (see HHE dated February 23, 2010) because of findings from the (b) (4) inspection described above related to microbial contamination. The request for the HHE consult (from the Office of Compliance, Division of Manufacturing and Product Quality) stated that during the recent FDA inspection and analysis of samples from (b) (4) *Bacillus cereus* was found in seven samples, and the *Bacillus cereus* enterotoxin was found in one sample. Preliminary microbiological results from the Pacific Regional Laboratory were provided; the highest levels measured were 240 Most Probable Number [MPN]/g in one sample, and 93 MPN/g in another sample; the remainder of the samples had levels of 43 MPN/g or less. (Levels of *Bacillus cereus* measured in MPN/g can be considered interchangeable with levels measured

in Colony Forming Units [CFU]/g.) The key conclusions of the HHE Review were as follows:

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

### 3.4 Fourth Review Cycle

In the fourth review cycle, the reviews of Drug Product, Non-Viral Drug Substance Issues, and Final Product Release and Packaging were conducted by Wei Guo, and the review of Microbiology was conducted by Stephen Langille. A CMC Secondary (Summary) review was conducted by Emanuela Lacana. 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.)

The CR Letter (see Appendix 12) cited a letter sent to the drug substance DMF holder, and minutes of a meeting with the drug substance DMF holder and the Applicant; it also included facility inspection deficiencies.

#### 3.4.1 DS Viral Issues (fourth cycle)

A DS Viral Issues Review was not conducted during the fourth review cycle because updates regarding DS viral issues were not provided in the DMF, and because the DS viral issues deficiencies identified in the third review cycle were deemed to not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's). (See Sections 3.3.1, 3.5.1, and 13.6 of this CDTL Review.)

#### 3.4.2 DS Non-Viral Issues (fourth cycle)

The overall findings of the DS Non-Viral Issues reviewer were that each of the deficiencies identified in the previous cycle 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 13): 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 3.4.5 of this CDTL Review).

### 3.4.3 DP Issues (fourth cycle)

The overall findings of the DP reviewer in the fourth review cycle were that deficiencies exist, but these do not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's). (See Sections 3.5.3 and 13.6 of this CDTL Review.)

### 3.4.4 Final Product Release and Packaging Issues (fourth cycle)

The overall findings of the Final Product Release and Packaging Reviewer in the fourth review cycle were that the deficiency item identified in the third cycle was adequately addressed.

### 3.4.5 Microbiology Issues (fourth cycle)

The overall findings of the Microbiology Reviewer in the fourth review cycle were 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 NDA 22-222 cannot be recommended for approval until the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) (see Appendix 13) 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 13): (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.

### 3.4.6 Facility Inspections (fourth cycle)

Eurand Inspection: Based on the Establishment Evaluation System (EES) report, there is an "Acceptable" recommendation from the Office of Compliance for Eurand dated August 19, 2008.

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation from the Office of Compliance for (b) (4) dated November 18, 2010. The reason stated in the Summary Report for NDA 22,222 is "EIR REV-NONCONCUR W/ DISTRICT" (EIR stands for Establishment Inspection Report). In addition, the OAI Status for (b) (4) in the Summary Report for NDA 22,222 is "Potential OAI" (OAI stands for "Official Action Indicated").

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation from the Office of Compliance for (b) (4)

(contract testing laboratory for (b) (4) dated September 22, 2010. The reason stated in the Summary Report for NDA 22,222 is “EIR REV-CONCUR W/ DISTRICT” (EIR stands for Establishment Inspection Report). In addition, the OAI Status for (b) (4) in the Summary Report for NDA 22,222 is “None.”

A summary of each of the observations cited in FDA Form 483 issued to (b) (4) and FDA Form 483 issued to (b) (4) (contract testing laboratory for (b) (4) is provided in Appendix 14.

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

### 3.5 Current Review Cycle

In the current review cycle, the Drug Product and Drug Substance reviews were conducted by Richard Ledwidge, and the Microbiology reviews were conducted by Stephen Langille. A CMC Secondary (Summary) review was conducted by Emanuela Lacana.

#### 3.5.1 DS Viral Issues (Current Cycle)

A separate DS Viral Issues Review was not conducted during the current (fifth) review cycle. The DS viral issues deficiencies identified in the third review cycle were deemed to not preclude approval of the application since these could be addressed as postmarketing commitments (PMC’s) (see Section 3.3.1 of this CDTL review).

#### **DS Viral Postmarketing Commitments (PMC’s):**

DS viral items to be communicated to (b) (4) (taken from Dr. Lacana’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.)

DS PMC #1: To provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility. Final report submitted [Insert date]

DS PMC #2: To develop and validate an infectivity assay for Porcine Circovirus 1 (PCV1). Final report submitted [Insert date]

DS PMC #3: To establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release. Final report submitted [Insert date]

DS PMC #4: To perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic

(b) (4)

viruses for monitoring by qPCR. An appropriate control strategy will then be implemented. Final report submitted [Insert date]

DS PMC #5: To 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, PTV, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria will be submitted to the Agency. Final report submitted [Insert date]

DS PMC #6: To assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality. Final report submitted [Insert date]

DS PMC #7: To revise 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 submitted [Insert date]

### **3.5.2 DS Non-Viral Issues (Current Cycle)**

The DS reviewer noted that a deficiency exists, but does not preclude approval of the application since it can be addressed as a postmarketing commitments (PMC). (See DS Review by Richard Ledwidge dated February 1, 2012 for complete information.)

The PMC recommended by the DS reviewer is provided below; this is followed by a summary of the DS reviewer's assessment of (b) (4) response to the deficiency item identified in the fourth review cycle, and the DS reviewer's assessment of additional pertinent information provided by (b) (4)

#### **DS Non-Viral Postmarketing Commitment (PMC):**

A DS non-viral item to be communicated to (b) (4) (taken from Dr. Lacana's review) as a postmarketing commitment (PMC) is provided below. (The numbering of the PMC corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

DS PMC #8: To 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 submitted [Insert date]

#### **(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 13) 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 two 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 12 months.
- (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.

**3.5.3 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 PMC's; it should be noted that the DP reviewer in the previous (fourth) review cycle also concluded that DP deficiencies could be addressed as PMC's.

PMC's recommended by the DP reviewer are provided below; this is followed by a summary of the DP reviewer's assessment of the response from Aptalis and (b) (4) to a deficiency item

identified in the fourth review cycle, and the DS reviewer's assessment of additional pertinent information provided by the Applicant.

**DP Postmarketing Commitments (PMC's):**

DP items to be communicated to (b) (4) (taken from Dr. Lacana's review) as 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.)

DP PMC #1: To revise release and stability specifications after [insert number] lots of drug product have been manufactured. Final report submitted [Insert date]

DP PMC #2: To include accelerated and/or stressed stability conditions in the annual stability protocol. The updated protocol will be provided by: [Insert date]

DP PMC #3: To evaluate stability of drug product manufactured using drug substance at the end of the shelf-life. Stability data will be provided by: [Insert date]

**Response from Aptalis and (b) (4) (Bacillus cereus Enterotoxin; Item #14):**

Below is a summary of the DP Reviewer's assessment of the response from Aptalis and (b) (4) addressing the issue of Bacillus cereus Enterotoxin (BCE) presence in pancrelipase API (see Item #14 in the Letter to (b) (4) Appendix 13). See also Section 3.5.5 of this CDTL Review.

BDE ELISA Test: The DP Reviewer concluded that because of the presence of (b) (4) and proteases in the pancrelipase API (that may lead to false positives and false negatives, respectively), the ELISA test is not suitable to detect BDE in the pancrelipase matrix; thus, another assay that is not subject to interferences in the pancrelipase API is required to detect BDE.

Other Comments: The DP Reviewer noted that the concentration of proteases in the API is such that it would degrade a late log/stationary phase Bacillus cereus culture producing BDE in (b) (4) therefore, any introduced BDE into the process will be destroyed. The DP Reviewer also commented that multiple in-process microbial controls are in place to ensure that BDE will not be produced by B. cereus during the manufacturing process.

Western Blot Methods to Detect BDE: To overcome the interference of the ELISA test, the Applicant developed Western Blot methods to detect BDE. The DP Reviewer summarized the results in pancrelipase API 25 mg/mL (approx. 8,500 USP Protease Units) as follows:

- 100 ng/mL BDE is degraded in < (b) (4) to below the BDE LOD (b) (4) ng/mL)
- 500 ng/mL BDE is degraded in (b) (4) to below the BDE LOD ( (b) (4) ng/mL)

The DP reviewer noted that the typical BDE concentration in the late log phase of a Bacillus cereus culture is (b) (4) ng/mL, and that durin (b) (4)

(b) (4) Thus, the DP Reviewer concluded that the studies demonstrate that any pre-formed BDE will be rapidly degraded during the manufacturing of pancrelipase API. The DP Reviewer commented that the results of the

studies using Western Blot Methods are consistent with the scientific literature, and that the risk of pre-formed BDE being administered to patients is negligible.

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

- production of BDE typically begins once cell density reaches (b) (4) cells/ml in rich media (but has been shown to occur at a minimal level of (b) (4) cells/gram)
- the FDA has set a risk threshold of  $10^6$  cells/g in food
- only (b) (4) show BDE production.

In process limits were set as follows:

- (b) (4)
- (b) (4)

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

Overall Recommendation: The overall recommendation from the DP Reviewer and the Secondary CMC Reviewer is that the Applicant has adequately addressed the concern about the risk of Bacillus cereus Enterotoxin (BCE) contamination.

**Additional Pertinent Information (Assay Transfer):**

Below is a summary of the DP Reviewer's assessment of the additional information provided by the Applicant regarding assay transfer for release and stability testing from (b) (4) to (b) (4)

The Agency was notified on November 15, 2011 that the transfer would go into effect by the end of 2011, and that this was due to the expected site closure of (b) (4)

Original Proposal: The Applicant's original proposal was to provide data to support the transfer of analytical methods (for release and stability testing) from (b) (4) to the (b) (4) testing site. The DP Reviewer concluded that the limited data provided by the applicant to support the transfer of analytical methods for release and stability testing were insufficient for the following reasons:

- The analysis of the data did not include a statistical assessment of the equivalency between the two laboratories (which is critical in providing assurance that similar results will be obtained at each testing facility).
- The use of a single lot of drug product does not evaluate the variability inherent between different test samples.

The DP Reviewer offered the following recommendations:

- While the transferred assays have been validated for linearity, specificity etc., a robust assay transfer study should also include different test samples to confirm the validation characteristics the assays are purported to possess.
- The Applicant should provide data on multiple lots of drug product to allow for a wider range of product characteristics and an analysis of the results demonstrating equivalency

between the two sites using appropriate statistical methodology (equivalency testing) with defined confidence intervals.

- The method transfer exercise should include justifications of acceptance criteria and sample sizes.

The Agency discussed the inadequacy of the Applicant's submitted method transfer exercise and a regulatory path forward for NDA 22222 in a teleconference that took place on January 30, 2012. The Applicant provided a revised proposal.

Revised Proposal: Aptalis proposed that instead of conducting a robust assay transfer exercise for (b) (4) they will use Aptalis Pharma SRL in Pessano con Bornago, Italy to perform DP release testing. Aptalis Pharma SRL is approved for all drug product release testing related to NDA 22222 except for HPLC and Karl Fischer testing. Aptalis reached an agreement with (b) (4) to continue to perform the HPLC and Karl Fischer testing at (b) (4). The DP Reviewer concluded that performing the HPLC and Karl Fischer tests at (b) (4) is acceptable. However, the DP Reviewer provided Aptalis with the option to perform the HPLC and Karl Fischer tests at (b) (4) as Aptalis initially planned. The DP Reviewer noted that although they typically expect a more robust assay transfer exercise for a HPLC impurity test and although the HPLC data showed slight bias upon moving it to (b) (4) the DP Reviewers concluded that the amount of variation observed between the two sites is acceptable. The DP Reviewer explained that a robust equivalency test is not required for this HPLC assay in part because the acceptance criteria for peak sizes are wide and thus there would not be much to be gained by performing equivalency testing. In addition, the HPLC assay is not measuring known attributes that have been linked to safety and efficacy, and thus the risk is considered negligible. The DP Reviewer noted that the data to support Karl Fischer testing at (b) (4) is also acceptable.

Overall Recommendation: The DP Reviewer concluded that it would be acceptable for DP release testing (except HPLC and Karl Fischer) to be performed at Aptalis Pharma SRL in Pessano con Bornago, Italy and for HPLC and Karl Fischer testing to be performed at either (b) (4) or (b) (4).

Applicant's Response: The Applicant sent a letter on February 3, 2012, that all Ultresa finished product release testing except for HPLC and Karl Fischer testing will be conducted at their Passano con Bornago, Italy site. HPLC and Karl Fischer testing will be conducted at (b) (4) ( (b) (4) (b) (4) (b) (4) ) will no longer be involved in drug product testing for Ultresa.

### 3.5.4 Final Product Release and Packaging Issues (Current Cycle)

No final product release and packaging issues were identified by the CMC reviewers in the current review cycle. Final product release and packaging issues were addressed in the fourth review cycle.

### 3.5.5 Microbiology Issues (Current Cycle)

The Microbiology Reviewer deemed the responses to each of the deficiency items in the letter sent to (b) (4) October 27, 2010 satisfactory. See Microbiology Reviews by Stephen Langille dated January 31, 2012 for complete information.

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

A summary of the Microbiology reviewer'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 13) 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 pancreas harvesting and (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) CFU/g.
- (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 (b) (4): 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) CFU/g for the (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), (b) (4) and (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) CFU TAMC/g, and stated that the response to this item is acceptable.

It should be noted that the Response to Item 14 in the Letter to (b) (4) (release test procedure for Bacillus cereus, and commitment to test each batch of DS for Bacillus cereus prior to release) was reviewed by the DP Reviewer (see Section 3.5.3 of this CDTL Review).

### 3.5.6 Facility Inspections (Current Cycle)

Recommendations from the Office of Compliance (based on the Establishment Evaluation System (EES) report) are as follows<sup>6</sup>:

- Aptalis Pharma SRL (formerly Eurand S.p.A.) (Pessano con Bornago, Italy) (DMF 15681): “Pending” status in EES at the time of this CDTL Review. The Office of Compliance will make a final recommendation by February 23, 2012.<sup>7</sup>
- All other facilities: “Acceptable” status in EES

The other facilities (as per a listing in the Addendum to the 356h form in Module 1 of the submission received February 7, 2012) are the following:

- (b) (4) (b) (4) (DMF (b) (4))
- (b) (4)
- (b) (4) (b) (4)

## 3.6 Final Recommendation

An Approval Action is the final recommendation by CMC. The final recommendation from the Office of Compliance on the Aptalis Pharma SRL (Pessano con Bornago, Italy) facility is pending, and will be made by February 23, 2012.

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

Nonclinical pharmacology/toxicology data were reviewed by the Nonclinical Pharmacology/Toxicology reviewer, David Joseph, 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<sup>8</sup>, 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 Ultresa clinical development

<sup>6</sup> Recommendations from the Office of Compliance are based on an 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 February 3, 2012.

<sup>7</sup> Verbal communication from Zhong Li at Meeting for Ultresa and Viokace NDA’s held on February 9, 2012.

<sup>8</sup> U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). “Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs.” <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf>> April 2006.

program. However, toxicology studies are needed if the excipients in the Ultresa 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 Ultresa 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 Ultresa.

The non-clinical information provided by the Applicant in the submission was mostly related to the excipients croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP-55), triethyl citrate, talc, and iron oxide because the daily intake for these excipients could exceed the maximum daily oral dose among all approved drugs products, as determined from the maximum daily dose of Ultresa, and from information from the FDA Inactive Ingredients Database.

Dr. Joseph's overall conclusion from the nonclinical review of the information submitted in the NDA was that the submitted toxicology information provides a reasonable assurance of safety for the estimated maximum daily dose of any excipient or phthalic acid that could result from Ultresa administration, and that an approval of the Ultresa NDA is recommended.

Dr. Joseph additionally recommended that the proposed labeling be revised as follows:

- Use in Specific Populations section (Pregnancy subsection): Wording should be revised to: Pregnancy Category C. "Animal reproduction studies have not been conducted with pancrelipase. It is not known whether pancrelipase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancrelipase should be given to a pregnant woman only if clearly needed." In addition, Dr. Joseph recommends the use of "pancrelipase" instead of "Ultrase MT Capsules" since the statements in this subsection are applicable to all pancrelipase products. Inclusion of a subheader "Teratogenic effects" should also be included prior to the "Pregnancy Category C" subheading, consistent with labeling regulations (21 CFR 201.57).
- Nonclinical Toxicology section (Carcinogenesis, Mutagenesis, Impairment of Fertility subsection): Wording should be revised to: "Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase."

## 4.2 Second, Third, Fourth, and Current Review Cycles

There were no new nonclinical pharmacology/toxicology data in the resubmissions, and no additional review of nonclinical data was performed in the second, third, fourth, and current review cycles.

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.

### 4.3 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 (CP-01; UMT20CP05-01; BA study): This was a randomized open-label single-treatment crossover study that evaluated the bioavailability of Ultresa-Eudragit (older formulation of Ultresa coated with Eudragit) and Ultresa-TbMP (Ultresa coated with HP-55) in 20 patients (10 chronic pancreatitis patients with EPI [CPPI] and 10 chronic pancreatitis patients without EPI [CP]) in gastric and duodenal aspirates under fed conditions. A single fixed dose of 46,000 USP lipase units (about 650 U/kg) was administered. Of the 20 patients, 11 patients (6 CPPI and 5 CP patients) had evaluable data. In CPPI patients (n=6), Ultresa-TbMP had higher mean percent recovery than Ultresa-Eudragit (43% vs. 27%, respectively). In CP patients (n=5), Ultresa-Eudragit had a higher mean percent recovery than Ultresa-TbMP (260% vs. 141%, respectively). Dr. Chen concluded that comparability of the two Ultresa formulations was not demonstrated in this study. It should be noted that the bioavailability study is not a required study for NDA approval.
- *In vitro* stability study (RE-071211-01; Stability study): The *in vitro* stability study was performed with the objective of demonstrating the *in vitro* stability of the minitablets (contents of the Ultresa TbMP capsules) over time when dispersed on food at room temperature. This study was requested by the Division in order to support the proposed labeling of the product for administration to young children who are unable to swallow intact capsules, so that the capsules may be opened and the minitablets sprinkled and mixed with a small quantity of soft food (e.g., applesauce). The results of the *in vitro* study show that 60 minutes after being sprinkled on soft foods (i.e., applesauce, pudding, and yogurt), the Ultresa TbMP minitablets' enteric coating remained functional. Sixty-minute dissolution testing in simulated gastric fluid (SGF) and then 30-minute dissolution in phosphate buffer (pH 6.0) showed that 92% to 98% of lipase was released (i.e., available for release in the duodenum). Thus, the *in vitro* stability study supports the proposed labeling claim for administration of Ultresa TbMP after opening the capsules and mixing the contents (minitablets) in soft acidic foods when intact capsules cannot be swallowed.

Labeling recommendations were also provided in Dr. Chen's review. Since Ultresa was not recommended for Approval during the initial review cycle, labeling changes were not negotiated with the Applicant.

## 5.2 Second Review Cycle

The reader is referred to the Clinical Pharmacology Review by Lucy Fang dated September 8, 2009, for complete information.

During the second review cycle, a concern was raised about the *in vitro* stability study and an information request was sent to the Applicant.

The concern raised was the following: Based on the product description, the enteric-coating of minitables in Ultresa Capsules is designed to dissolve at  $\text{pH} \geq 5.5$  which allows delivery of the enzymes to the duodenum. However, it was shown in the *in vitro* stability study that the minitables were stable in chocolate pudding (approximate  $\text{pH}$  6.4) with mean remaining enzymatic activity of 101% and 95% after incubation with pudding for 30 and 60 minutes, respectively. Thus, a concern was raised about the validity of the *in vitro* stability study.

The Applicant was requested to explain this observation and provide data from the control samples in the same study (i.e., minitables subject to the same conditions but without being mixed with chocolate pudding).

The explanation offered by the Applicant is summarized as follows:

- The dissolution test was conducted at room temperature, and based on the Arrhenius equation (relating temperature and chemical reaction rates) for every  $100^{\circ}\text{C}$  decrease in temperature, a 2-3 fold decrease in reaction rates is predicted; this would slow down the ionization of the polymer, and its solubilization when compared to the dissolution test temperature of  $37^{\circ}\text{C}$ .
- The pudding is a relatively viscous medium where molecular diffusion of the aqueous phase is reduced when compared to a buffered solution.
- Puddings are formulated with cellulosic polymers that capture a significant amount of water reducing the amount of free unbound water available for the enteric polymer ionization and dissolution; and
- Although each mini-tablet was in contact with food, there was no mixing during the test. In the absence of mixing, an acidic stagnant diffusion layer would exist around each minitabulet reducing the dissolution rate of the enteric polymer.

The Clinical Pharmacology Reviewer found the Applicant's response acceptable, but recommended specific label language for mixing with food as follows:

- (1) The Ultresa minitables can only be mixed with acidic food ( $\text{pH} < 5.5$ ).
- (2) Mixing temperature should be room temperature.
- (3) The mixing process should be short (seconds) and the medicine should be taken right after the mixing.

### **5.3 Third, Fourth, and Current Review Cycles**

There were no new clinical pharmacology data in the resubmissions, and no additional review of clinical pharmacology data was performed in the third, fourth, and current review cycles.

The recommendations for labeling revisions from the initial and second review cycles were negotiated with the Applicant during the current review cycle. The labeling revisions included changes to the Dosage and Administration section and the Clinical Pharmacology section.

### **5.4 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 Ultresa 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 July 1, 2008, the Clinical Review by Joanna Ku dated July 1, 2008, and the Statistical Review by Stella Grosser dated June 25, 2008, for complete information.

The Applicant conducted a single pivotal study (UMT20CF05-01) using the TbMP formulation. It should also be noted that other studies were conducted using the Eudragit formulation (see Dr. Pariser's CDTL Review).

Study UMT20CF05-01 was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of Ultresa TbMP administered to 31 patients with CF and EPI, ages 8 to 37 years. The study involved a Screening Period (up to 11 days), two Treatment Periods (6-7 days) each preceded by a Stabilization Period (4 days) and separated by a Break Period (3-6 days). Doses were not to exceed 2,500 lipase units/kg/meal or snack.

Efficacy was assessed by the difference in a 72-hour fecal fat collection (CFA) during Ultresa TbMP treatment as compared to placebo treatment. %CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet, and is calculated by:

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

The results of the study show that of the 36 patients that were screened, 32 patients were enrolled, and 31 were randomized into the study. Of the 31 patients who were randomized (ITT population), 28 patients had at least one evaluable CFA, and 24 patients completed both treatment periods of the study and had CFA results available for each treatment period. Fourteen (14) patients were randomized to treatment sequence 1 (Ultresa TbMP → placebo), and 17 patients to treatment sequence 2 (placebo → Ultresa TbMP). Compliance with study medication was high (>97%) overall and during both DB treatment periods.

The mean age of study patients (ITT population, n=31) was 20 years (range 8 to 37 years), and 45% of patients were 18 years of age or younger. There was a predominance of males in the study (65%), and 94% were Caucasian, which is consistent with the racial/ethnic prevalence of the disease. Most patients were on multiple medications at study entry, which were continued during the study, most commonly multivitamins and respiratory agents (e.g., dornase alfa or beta-adrenergic agonists). Proton pump inhibitors (PPIs) or other medications that alter gastric pH could be used during the study.

The primary efficacy endpoint results showed that mean CFA for patients during placebo treatment was 56%, and during Ultresa TbMP treatment was 89%. The difference in mean CFA on Ultresa TbMP as compared to placebo was 34%, which was a clinically meaningful and statistically significant difference ( $p < 0.0001$ ). The results are summarized in the table below.

**Table 3. Pivotal Study (CF-01), Primary Efficacy Endpoint Results**

Parameter	Statistic	Treatment		Delta
		Ultresa <sup>®</sup> MT20	Placebo	
Number of Patients in the ITT Population	N	30	31	30
CFA%	n	25	27	24
	Mean	88.550	55.614	34.742
	STD	4.943	25.104	25.049
	Median (Min., Max.)	89.190 ( 77.36, 97.08)	51.950 ( 13.59, 97.12)	40.385 ( -7.24, 75.22)
Mixed Model Fixed Effect [a]				
Sequence	p-value	0.9060		
Period	p-value	0.3204		
Treatment Group	p-value	<0.0001**		
Note: n for CFA% includes all randomized patients who completed at least one treatment period; the delta value is the mean of the individual treatment differences in patients who completed both treatment periods.				

Table above is taken from CDTL Review by Anne Pariser dated July 1, 2008

A subgroup/sensitivity analysis was performed by the Clinical Reviewer (Dr. Ku) for change in CFA by placebo-treatment (no-treatment) CFA, where patients were evaluated by the following no-treatment CFA subgroups:

- severely-affected (CFA  $\leq$ 40%),
- moderately-affected ( $>$ 40 and  $\leq$ 80%), and
- mildly-affected ( $>$ 80%).

The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of  $\leq$ 40%. There are no generally accepted definitions for moderately- versus mildly-affected patients, and these cut-points were arbitrarily selected.

In severely-affected patients, an increase in CFA of  $\geq$ 30% is accepted as being clinically meaningful; however, for the moderately- and mildly-affected patients, there is no generally accepted change in CFA that is considered as being clinically meaningful.

The subgroup results are summarized below:

- For the severely-affected patients (n=6), the mean CFA during placebo treatment was 24%, mean CFA during Ultresa TbMP treatment was 89%, and the mean difference on Ultresa as compared to placebo was 65%. This difference between the two treatment periods is clinically meaningful, although it is noted that the number of patients in this subgroup is small.
- For the moderately-affected patients (n=12), the mean CFA during placebo treatment was 51%, mean CFA during Ultresa treatment was 87%, and the mean difference on Ultresa as compared to placebo was 36%, which also appears to be clinically meaningful.
- For the mildly-affected patients (n=6), the mean CFA during placebo treatment was 89%, mean CFA during Ultresa treatment was 92%, and the mean difference on Ultresa as compared to placebo was 3%. This difference may not be clinically meaningful; however, it is noted that all patients in this subgroup had a CFA during placebo treatment  $>$ 85% and half the patients had a CFA  $>$ 90% during placebo treatment, and therefore, had little capacity to respond to active PEP treatment.

Thus, the change in CFA results during Ultresa treatment correlated strongly with placebo-CFA; i.e., patients with lower CFA while on placebo had the greatest increases in CFA on Ultresa treatment, and those with higher placebo-CFA had smaller changes.

The Clinical Reviewer also performed assessments by demographic factors, including age and gender; there were too few non-Caucasian patients to assess the results by race. No obvious effects on the overall results of the study were seen by the Clinical Reviewer for any of these factors; however it is noted that the subgroups are small.

There is considerable clinical experience with the formulation of Ultresa that was studied in the pivotal study. In addition, there is considerable clinical experience with similar formulations of porcine-derived PEPs.

## 7.2 Second, Third, Fourth, and Current Review Cycles

In the second review cycle, data were submitted from an open label study (UMT20CF07-01) conducted in nine patients ages 7 to 11 years with EPI due to CF. The study was conducted

at three US sites, and included a screening phase on individually-titrated Ultresa doses not to exceed 2,500 lipase units/kg/meal (15 days), a washout (no-treatment) phase (7 days), followed by a treatment phase on the same individually-titrated Ultresa dose (12 days). The primary analysis was the difference in CFA assessed during the washout phase and treatment phase.

Of the nine patients that were screened, two patients discontinued during the washout phase leaving seven patients that completed both the washout and treatment phases of the study. The mean daily dose of Ultresa was 6,361 lipase units/kilogram/day during the last 4 days of the screening phase, and was 6,846 lipase units/kilogram/day during the treatment phase. The mean duration of the treatment phase was 5.7 days. All patients consumed a high-fat diet (2 grams of fat per kilogram of body weight per day) during both the washout phase and the treatment phase. The seven patients were all male. Six patients were Caucasian and one patient was African-American. The patients ages were 7 to 11 years (mean age 10 years). The mean ( $\pm$ SD) CFA during the washout phase was 34.5% ( $\pm$  21.3%), and during the Ultresa treatment phase was 82.7% ( $\pm$ 13.3%). See table below.

**Table 4. CFA in Patients that Completed the Washout Phase and Treatment Phase (n=7)**

Statistic	Washout Phase <sup>A</sup> (n=7)	Treatment Phase (n=7)	Change <sup>B</sup>
Mean	34.5	82.7	48.2
SD	21.35	13.25	25.94
Median	42.0	85.1	42.3
Min., Max.	-2.2, 54.9	54.5, 92.9	12.5, 87.3
p-value <sup>C</sup>	0.0013**		
p-value <sup>D</sup>	0.0078**		

\* Indicates statistical significance at the 0.050 level; \*\* Indicates statistical significance at the 0.010 level.

A Free of exogenous pancreatic enzymes.

B For each patient, change is the change from his/her Washout Phase CFA (%) value to his/her Treatment Phase CFA (%) value.

C p-value from a paired t-test comparing Treatment Phase mean CFA (%) and Washout Phase mean CFA (%).

D p-value from a Wilcoxon signed rank test comparing Treatment Phase mean ranked CFA (%) and Washout Phase mean ranked CFA (%).

Table above modified from Table 14.2.1.1.1 of the UMT20CF07-01 Study Report.

Patients with a baseline CFA < 40% showed greater increases in CFA after treatment with Ultresa than patients who had a washout CFA  $\geq$ 40%. The mean change in CFA was 72.4% in the three patients with washout CFA < 40%, and was 30.2% in the four patients with washout CFA  $\geq$  40%. See table below.

**Table 5. CFA in Subgroups Based on Washout CFA\***

Washout CFA Subgroup	Washout Phase CFA	Treatment Phase CFA	Change in CFA
Washout CFA <40% (n=3)	13.9 ( $\pm$ 14.3)	86.2 ( $\pm$ 6.2)	72.4 ( $\pm$ 16.0)
	18.6 (-2.2, 25.2)	85.1 (80.7, 92.9)	74.3 (55.5, 87.3)
Washout CFA $\geq$ 40% (n=4)	49.9 ( $\pm$ 5.6)	80.1 ( $\pm$ 17.4)	30.2 ( $\pm$ 12.6)
	51.5 (42, 54.8)	86.5 (54.5, 92.9)	33.0 (12.5, 42.3)

\*Mean ( $\pm$ SD) and Median (Min, Max) shown

Table above generated by this reviewer using dataset CV\_EFF provided in the submission.

No additional efficacy data were submitted in the third, fourth, and current review cycles.

### 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 July 1, 2008, the Clinical Review by Joanna Ku dated July 1, 2008, the Clinical Reviews of Safety Updates by Ali Niak, dated September 9, 2009, March 9, 2010, April 30, 2010, and November 10, 2010, and by Marjorie Dannis, dated 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.<sup>9,10,11</sup> (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:

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<sup>9</sup> 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.

<sup>10</sup> 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.

<sup>11</sup> 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.

- 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.<sup>12,13</sup> (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 July 1, 2008, and the Clinical Review by Joanna Ku dated July 1, 2008, for complete information.

In the initial review cycle, the AE profile of Ultresa 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 Second, Third, and Fourth Review Cycles

The reader is referred to the Safety Update Clinical Reviews by Ali Niak, dated September 9, 2009 (for the second review cycle), dated March 9, 2010 and April 30, 2010 (for the third review cycle), and dated November 10, 2010 (for the fourth review cycle) for complete information.

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<sup>12</sup> Antiviral Drugs Advisory Committee (December 2, 2008);  
<<http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs>>

<sup>13</sup> Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

In the second, third, and fourth review cycles, the AE profile of Ultresa as described in the clinical study update and in the postmarketing experience 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 second, third, and fourth review cycle safety updates.

A summary of the Safety Update Clinical Reviews for the second, third, and fourth review cycles can be found in the CDTL Reviews for the initial, second, third, and fourth review cycles, dated July 1, 2008, September 9, 2009, May 5, 2010, and November 24, 2010, respectively.

### 8.3 Current Review Cycle

The reader is referred to the Clinical Review of Safety Update by Marjorie Dannis, dated December 20, 2011 for complete information.

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. The Applicant provided safety information from post-marketing experience and from the clinical study update.

Postmarketing Experience: Dr. Dannis notes that based on Canadian unit sales of Ultrase® MT Capsules during the reporting period (May 1, 2010, to June 30, 2011), patient exposure was estimated to be approximately 34,120 patient-treatment-days. Assumptions for this estimate were that patients would be consuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of three meals and two snacks per day, and patients would have an average weight of 54.3 kg (average weight for a 16 year old representing the 30<sup>th</sup> percentile); weight was selected based on age and weight data in the Cystic Fibrosis Foundation (CFF) Registry.

A total of six case reports of adverse events were reported; five of these reports involved Ultrase and one involved an unspecified brand of pancrelipase. Two serious cases were reported (the first case involving Ultrase, and the second involving an unspecified brand of pancrelipase).

- The first serious case was the occurrence of breast cancer, post-surgical infection and diarrhea in a 58 year old female. The medical history was not reported. The primary clinical reviewer noted that there is a reasonable possibility for a causal relationship between Ultrase and diarrhea because of the disappearance of diarrhea after switching from Ultrase to Creon. The primary clinical reviewer also noted that there is no reasonable possibility for a causal relationship between breast cancer and Ultrase because of the absence of biological plausibility; similarly, there is no reasonable plausibility for a causal relationship between post-surgical infection and Ultrase because this event was a procedural complication.
- The second serious case was the occurrence of commensal bacteria induced necrotizing pancreatitis, gallstone pancreatitis, pleural effusion and elevated alanine aminotransferase

/ alkaline phosphatase levels in a 68-year-old male. The patient's medical history included hypertension, atrial fibrillation, gout, chronic kidney disease and dyslipidemia. There was no history of alcohol or tobacco use. Co-suspected medications included warfarin, amlodipine and atenolol. The primary clinical reviewer noted that the diagnosis was medically confirmed, that the patient was treated with penicillin and trimethoprim/sulfamethoxazole for the organisms identified, that the patient underwent surgery after 4 weeks, and returned to his usual state of health 2 weeks after discharge from a rehabilitation facility. Although the start date of pancrelipase relative to the onset date of the event is not known, it is likely that the patient had been prescribed pancrelipase for the gallstone pancreatitis as per the Applicant. For this reason, and because of the absence of biological plausibility, there is no reasonable possibility for a causal relationship between pancrelipase and any of the AEs in this case.

There were a total of 19 AEs with Ultrase MT. Other than the AEs described in the serious case with Ultresa above, these included two occurrences of abdominal pain and diarrhea, and single occurrences of the following AEs: nausea, oral discomfort, oral pain, retching, vomiting, aggravated concomitant disease, ineffective drug, hypersensitivity, increased pancreatic enzymes, trismus, burning sensation, headache, and oropharyngeal pain.

The pattern of common adverse events appeared to be similar to that described in the labeling for the three available approved PEPs (Creon, Zenpep, and Pancrease).

Clinical Study Update: A safety update was provided for Study UMT12CF08-01, a study of 45 CF patients aged 2 to 6 years old. The mean ( $\pm$ SD) exposure was 20.0 ( $\pm$ 3.5) days in the treatment phase. The adverse events were most commonly reported in the gastrointestinal (GI) and respiratory systems, tended to reflect underlying disease, and were consistent with the previously known safety profile of the product. No deaths or SAEs were reported during the study.

Literature Update: The Applicant conducted a search of the medical literature for the period from May 5, 2010, to June 31, 2011. A proof-of-concept study was conducted in 42 CF patients ages 10 to 36 years to explain the reason of failure of pancreatic enzymes treatment to completely correct malabsorption and gastrointestinal symptoms in CF patients.<sup>14</sup> Capsule endoscopy was used in 28 patients with pancreatic insufficiency (PI) and 13 patients that were pancreatic sufficient(PS); a high prevalence of small bowel injury in CF patients was observed (both in patients with PI and in patients who were PS). The study suggested a condition compatible with a "CF-bowel" that may explain the persistence of malabsorption and gastrointestinal symptoms in CF patients.

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<sup>14</sup> Werlin SL et al. 2010. Evidence of intestinal inflammation in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 51(3):304-8.

## 8.4 Final Recommendation

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

It should be noted that although a REMS was recommended in the previous review cycles, a REMS is no longer recommended for Ultresa. This is consistent with the other approved PEPs (see Sections 2.2.1 and 13.3).

## 9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

## 10. Pediatrics

### 10.1 Initial, Second, and Third Review Cycles

During the course of the review in the third review cycle, a key issue was identified by the reviewer from the Division of Medication Error and Prevention Analysis (DMEPA), Denise Baugh, namely that the smallest dosage strength formulation of Ultresa may not be adequate for dosing infants and lower body weight children (see DMEPA Label and Labeling Review by Denise Baugh dated April 15, 2010). The general schema used for the previously approved PEPs was presented at the Pediatric Research Committee (PeRC) on March 24, 2010. A consult with the Pediatric Maternal Health Staff (PMHS) was obtained subsequent to the meeting 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 Ultresa.

#### 10.1.1 Pediatric Research Committee (PeRC)

The general schema used for the previously approved PEPs was proposed at the Pediatric Research Committee (PeRC) on March 24, 2010, as follows (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.

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

In addition, it should be noted that published literature data with PEPs in general, not necessarily data with the particular formulation (i.e., Ultresa), 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., Ultresa) comes from the randomized double-blind placebo-controlled cross-over study using that formulation (i.e., UMT20CF05-01) 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, UMT20CF05-01; can be considered to be a “bridging study” to the existing body of evidence from the literature for a range of pancreatic enzyme formulations.

#### **10.1.2 Consult with Pediatric and Maternal Health Staff (PMHS)**

The Pediatric and Maternal Health Staff (PMHS) was consulted because the smallest dosage strength formulation of Ultresa contains 13,800 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). For example, for an infant to receive the prescribed dose (2,000-4,000 USP units of lipase per each feeding of formula or breastmilk), according to the CFF guidelines, one would have to quarter the dose. In contrast, Pancreaze, Zenpep, and Creon (the previously approved PEPs) provide smaller doses (4,200, 5,000 and 6,000 USP units of lipase respectively), so splitting the dose in smaller fractions than one-half would not usually be necessary to provide an approximate dose to infants and lower body weight children.

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 13,800 USP units of lipase as the contents would have to 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 13.8 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. The PMHS reviewer noted that based on median weight in growth charts, there would be a substantial number of patients in the age 12 months and older to less than 4 years category that are under 13.8 kg. (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 27.6 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 PMHS reviewer noted that based on median weight in growth charts, there would be a substantial number of patients in the age 4 years and older category that are under 27.6 kg. (See also Appendix 14: Dosing Calculations - Children 1 to 10 Years Old)

The following label revisions are recommended: (1) The dosing recommendations for infants section should be deleted. (2) For children older than 12 months to less than 4 years, a statement should be added that children weighing under 14 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 28 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

## 10.2 Fourth and Current (Fifth) Review Cycles

In the fourth and current (fifth) review cycles, it was determined that it would not be necessary to present the application again to the Pediatric Research Committee (PeRC). The recommendations for labeling revisions from the third review cycle were negotiated with the Applicant during the fourth and current (fifth) review cycles.

## 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. Ultresa is not systemically absorbed.

### 11.2 Division of Scientific Investigations (DSI) audits

In the initial review cycle, site inspections of two clinical sites 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 CF-01. 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 6. Overview of two sites inspected (Study CF-01)**

Site Number/ Investigator / Location	No. pts enrolled	Inspector's key findings
Site 02 Theodore Liou, MD Salt Lake City, UT	Seven	<u>Protocol violations:</u> (a) Four patients allowed in the study before getting their fecal elastase results (inclusion criterion for entry). (b) At the beginning of the study, the dietician was sick and no replacement dietician was used; this resulted in poor dietary control and deviation from the dietary requirements for the protocol. <u>Overall assessment:</u> The data from this site can be used in support of the NDA.
Site 03 Steven Strausbaugh, MD Cleveland, OH	Six	<u>Minor protocol violations:</u> Two patients enrolled before results of fecal elastase results available; results later found to be within the protocol requirement. <u>Overall assessment:</u> The data from this site can be used in support of the NDA.

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

Because the protocol violations at each of the sites did not affect the validity of the data or markedly affect the calculation of the CFA (primary efficacy endpoint), the overall assessment of the inspector from the inspection of the two clinical sites was that the data are reliable and can be used in support of the NDA.

### **11.3 Drug Shortage**

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

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

### **11.4 Administration via Gastrostomy Tubes**

PEPs, including Ultresa, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Pancreaze via 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 “Ultrase MT” was submitted. A review of the trade name “Ultrase MT” was performed by Denise Baugh 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 ““Ultrase MT” unacceptable (under 21 CFR 201.10(c)(5)) due to the potential for confusion with another marketed product Altase and with the parent drug Ultrase, which could lead to medication errors. Another reason cited by DMEP to object to the proposed proprietary name was that Ultrase contains the USAN stem “-ase”, which is inconsistent with the USAN Council’s intent that USAN stems be reserved for established names only. DMEP also noted that the use of letter and numeric suffixes (e.g., MT20) are discouraged by DMEP, as they are ambiguous and unclear, and can be misinterpreted, which can also lead to medication errors.

A letter was sent to the Applicant during the review cycle (dated June 24, 2008) notifying the Applicant that the proposed trade name “Ultrase MT” was unacceptable and requesting submission of two alternative trade names. At the end of the initial review cycle, no trade name had been agreed upon with the Applicant.

### **12.1.2 Second Review Cycle**

In the second review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of “Ultrase MT” was unacceptable. Please see Proprietary Name Denied Letter (dated June 10, 2009) for complete information.

The Applicant submitted proposed proprietary names: “Ultrase MT 13,800,” “Ultrase MT 20,700,” and “Ultrase MT 23,000;” and alternate proprietary names “Ultrase 13,800,” “Ultrase 20,700,” and “Ultrase 23,000.” (Correspondence from the Applicant requesting review of the proposed proprietary names was received April 7, 2009.)

The reasons cited for the proposed proprietary names being unacceptable were the following (see Proprietary Name Denied Letter dated June 10, 2009):

- (1) Ultrase contains the USAN stem “-ase”, which is inconsistent with the USAN Council’s intent that USAN stems be reserved for established names only.
- (2) The modifier “MT” does not have a well recognized and consistent meaning among healthcare professionals and patients. The modifier “MT” (representing “mini-tablets”) does not convey any meaningful information to healthcare practitioners and thus is ambiguous. Modifiers are typically reserved to communicate a difference in formulation from currently marketed products within the same product line; since there is no other product(s) marketed within this same product line that would require the necessity to differentiate this name with the addition of a modifier, the letters “MT” do not communicate any information needed to prescribe or dispense the proposed product.
- (3) The numerical portion of the modifier is unacceptable because the Agency has determined that all three enzymes (lipase, protease, and amylase) are considered active ingredients, and the proposed numbers represent only the lipase component of the product, thus the use of such numbers would be misleading [under 21 CFR 201.6 (b)].

The Applicant was recommended to submit an alternate proprietary name for review.

The Applicant submitted two new names (primary name “Ultresa” and alternate name “(b) (4)”) on July 7, 2009. The review of those names was still under review at the time of the second action, but a decision on the name was made prior to the PDUFA date of October 7, 2009. DMEPA concluded that the proprietary name of “Ultresa” was acceptable. Please see Proprietary Name Granted Letter (dated October 5, 2009) for complete information.

### **12.1.3 Third Review Cycle**

The proprietary name “Ultresa” was deemed acceptable before the start of the third review cycle (see above).

A label and labeling review was performed by Denise Baugh in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated April 15, 2010). In addition to a Failure Mode Effects Analysis, an Adverse Event Reporting System (AERS) Database search was conducted because the product was currently marketed. The DMEPA reviewer noted that the AERS search conducted on March 8, 2010, yielded no relevant cases. [The following terms were used in the AERS search: Established Name “Pancrelipase”, Verbatim Name “Pancrel%” and the MedDRA reactions, “Medication Errors” (HLGT) and “Product Quality Issues” (HLGT).]

#### **12.1.4 Fourth Review Cycle**

There was no additional discussion of the proprietary name in the fourth review cycle. The proprietary name “Ultresa” was deemed acceptable before the start of the third review cycle (see above).

#### **12.1.5 Current Review Cycle**

In the current review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of “Ultresa” was acceptable. See DMEPA Proprietary Name Review (dated December 6, 2011) by Manizheh Siahpoushan and Proprietary Name Granted Letter dated December 19, 2011.

The proposed proprietary name Ultresa was re-reviewed 90 days prior to the approval of the NDA in accordance with the Proprietary Name Granted Letter (dated October 5, 2009). The reviewer concluded that the results of the Failure Mode Effects Analysis showed that the proposed name, Ultresa, is not vulnerable to name confusion that could lead to medication errors with any of the 53 names that were identified as having orthographic, phonetic, or spelling similarity to the proprietary name Ultresa.

### **12.2 Office of Prescription Drug Promotion Comments**

The Office of Prescription Drug Promotion Comments (OPDP) [formerly the Division of Drug Marketing, Advertising and Communications (DDMAC)] found the proposed proprietary names (“Ultresa” and “(b) (4)”; from the submission received July 7, 2009) acceptable from a promotional perspective; an e-mail stating this was sent from Nina Ton, Safety Regulatory Project Manager OSE on July 22, 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 drugs in the class that were recently approved, (Creon, Zenpep, and Pancreaze). 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 pending the final Office of Compliance recommendation (to be made by February 23, 2012) on the Aptalis Pharma SRL (Pessano con Bornago, Italy) facility.

### **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**

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 Ultresa (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 [Insert Date].

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 Ultresa (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

The timetable you submitted on [Insert Date] states that you will conduct this study according to the following timetable:

**Final Protocol Submission: by [Insert Date]**  
**Study Completion Date: by [Insert Date]**  
**Final Report Submission: by [Insert Date]**

2. An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in cystic fibrosis patients taking Ultresa (pancrelipase) Delayed-Release Capsules compared with an appropriate control group.

The timetable you submitted on [Insert Date] states that you will conduct this study according to the following timetable:

**Final Protocol Submission: by [Insert Date]**  
**Study Completion Date: by [Insert Date]**  
**Final Report Submission: by [Insert Date]**

### 13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

Clinical:

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

Drug Product:

- (1) To revise release and stability specifications after [insert number] lots of drug product have been manufactured. Final report submitted [Insert date]
- (2) To include accelerated and/or stressed stability conditions in the annual stability protocol. The updated protocol will be provided by: [Insert date]
- (3) To evaluate stability of drug product manufactured using drug substance at the end of the shelf-life. Stability data will be provided by:[Insert date]

Drug Substance:

- (1) To provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility. Final report submitted [Insert date]
- (2) To develop and validate an infectivity assay for Porcine Circovirus 1 (PCV1). Final report submitted [Insert date]
- (3) To establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release. Final report submitted [Insert date]

- (4) To perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy will then be implemented. Final report submitted [Insert date]
- (5) To 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, PTV, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria will be submitted to the Agency. Final report submitted [Insert date]
- (6) To assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality. Final report submitted [Insert date]
- (7) To revise 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 submitted [Insert date]
- (8) To 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 submitted [Insert date]

### **13.7 Recommended Comments to Applicant**

None.

## APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995<sup>15</sup>) are provided below:

“Infants may be given 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding. Although it makes physiologic sense to express doses as lipase units per gram of fat ingested, a weight-based calculation is a practical substitute beyond infancy. Enzyme dosing should begin with 1000 lipase units/kg per meal for children less than age four years, and at 500 lipase units/kg per meal for those older than age 4 years. Enzyme doses expressed as lipase units per kilogram per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two or three snacks per day.

If symptoms and signs of malabsorption persist, the dosage may be increased by the CF center staff. Patients should be instructed not to increase the dosage on their own. There is great interindividual variation in response to enzymes; thus a range of doses is recommended. Changes in dosage or product may require an adjustment period of several days. If doses exceed 2500 lipase units/kg per meal, further investigation is warranted (see discussion of management of CF, below). It is unknown whether doses between 2500 and 6000 lipase units/kg per meal are safe; doses greater than 2500 lipase units/kg per meal should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of absorption.

Doses greater than 6000 lipase units/kg per meal have been associated with colonic strictures in children less than 12 years of age, whether standard-strength enzymes or high-strength pancreatic enzymes were taken. Patients currently receiving higher doses should be examined and the dosage either immediately decreased or titrated downward to a lower range.”

Borowitz et al. 2002<sup>16</sup> states:

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

Fitzsimmons et al. 1997<sup>17</sup> 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

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<sup>15</sup> 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.

<sup>16</sup> 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.

<sup>17</sup> 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: DS Deficiency Items – First Action

Deficiencies in Drug Substance - including Virology (from DMF Deficiency Letter sent to (b) (4) dated July 1, 2008; Master File # (b) (4))

### CMC for Drug Substance:

1. The amount of raw materials used in manufacturing drug substance should be clearly defined. Limits should be placed on all process-related impurities in drug substance or alternatively, their removal by the process must be validated.
2. Please provide acceptance criteria for lipase, amylase, and protease specific activities, (b) (4) content and microbial limits for (b) (4). Storage conditions, expiration dating and data to support the stability should be provided.
3. Please provide data to support the operating parameters and performance parameters used in manufacturing process for 1208 and 1286. Please establish an acceptance range of yield for each critical manufacturing step and provide information supporting this range.
4. During November 1, 2005 – October 31, 2006 one 1208 lot failed microbial specifications and this lot was reprocessed and released. Please note that FDA approved drug products manufactured using reprocessed drug substance can only be released upon FDA approval or using a protocol previously approved by the FDA.
5. Please establish in-process control testing acceptance criteria for lipase activity and microbial limits before and after the enzyme activation and provide a justification for your approach.
6. Please provide results of a (b) (4) characterization study using olive oil as substrate.
7. Drug substance characterization report for amylase should be provided.
8. Please revise your (b) (4) API drug substance (1286) release and stability testing specifications to include a validated HPLC analysis method with acceptance criteria for the various peaks observed.
9. Tests for (b) (4) content, product-related substances and impurities, including degradants, should be added to drug substance release and stability testing. Please provide your revised specifications and data supporting your proposed changes.
10. The acceptance criteria of protease and amylase activity of (b) (4) API (1286 drug substance) are too wide to ensure the consistent manufacture of drug product. We recommend that the acceptance criteria for protease and amylase activity of (b) (4) API (1286 drug substance) be tightened. Please see ICH Q6B for guidance on setting specifications.
11. Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) quantity and activity should be ensured in drug substance. Please provide information that demonstrates you have control of (b) (4)

12. Provide characterization information for the olive oil used in your lipase activity assay of drug substance. Provide information on the routine qualification of the lots of olive oil to ensure the consistency of the assay results.
13. Please provide data that demonstrate that the enzymatic assay methods are performed such that the reaction product generated is linear respect to time.
14. Please provide data that demonstrate that other components in drug substance do not interfere with your enzymatic potency assays. This can be confirmed by (b) (4) into the drug substance.
15. Please provide data to support that the assays validated for drug product release and stability are suitable to assay drug substance.
16. Provide additional stability data for 1208 and 1286 drug substances made in 2006 and 2007, and the trend of all stability data to give the 95% confidence interval about the trending line.
17. Please identify an expiry or hold time for 1208 drug substance before (b) (4) and provide the data supporting your proposal.
18. Please establish an expiry for (b) (4) API (1286 drug substance) based on relevant stability data and provide the data supporting your proposal.
19. Please provide your drug substance release test sampling plans.

**Control of Adventitious Viral Agents:**

1. You have not provided an adequate description of your risk mitigation plan for control of adventitious agents. Please provide the following:
  - a. Describe in detail your plans for animal disease surveillance, including how emerging viruses will be assessed and controlled.
  - b. Please comment on the risk to product quality due to the potential infection of swineherds with parasites.
  - c. A detailed description of the sanitizing/cleaning procedures in place to prevent cross contamination between different batches of drug substance.
  - d. A detailed description of your plan on how to prevent cross contamination with material from other species, particularly ruminant tissues.
  - e. You stated that the pig pancreas glands are from slaughterhouses in the (b) (4) and that the pigs are raised with the intention of human food consumption. Please clarify whether pancreatic glands are harvested from swine born in these regions, or from swine imported into and slaughtered in these regions. In the latter case, please provide information on the country of origin of the swine.

f. Provide a summary of your pancreatic tissue vendor qualification/evaluation program for the last 4 years. The summary should include:

1. Name and dates of all pancreatic tissue vendor audits.
2. Quality systems evaluated.
3. A representative Health Certificate for animal by-products from each of approved vendors.

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

- a. According to ICH Q5A, because of the inherent variability of the viral clearance studies, results should be obtained from two independent experiments. However, the viral inactivation studies submitted were not performed as recommended, but rather used material from the same sample in duplicate and not from independent sources. Please provide information on the process's capacity to inactivate viruses from two independent experiments.
- b. Although you stated that you have initiated an evaluation of the (b)(4) step and the (b)(4) step for viral inactivation, you have not provided the results of this evaluation. This information is critical for the assessment of your overall plan for control of adventitious agents. Please provide the results from these studies together with any proposed changes in your viral control strategy. Please be aware that because the (b)(4) step and the (b)(4) step share the same components potentially responsible for viral inactivation (i.e., (b)(4)), this may lead to an overestimation of viral inactivation when adding the clearance values obtained from each individual process step. Please include data demonstrating which mechanism of inactivation is responsible for the calculated viral inactivation associated with each process step.
- c. Please provide a detailed description of the procedures used in the evaluation of the viral inactivation steps that contribute to the overall inactivation of these agents and include a discussion on the similarity of the lab scale process to the commercial process.
- d. Please provide a detailed description of the viral infectivity test procedures used for the evaluation of the (b)(4), (b)(4) steps.
- e. Although an evaluation of the toxicity of the test sample on the indicator cells has been performed, no information on assay interference was provided to support the dilution factors used for the determination of viral titers. Please submit a description of the experiments performed and results obtained for the evaluation of assay interference for test samples from the (b)(4) process steps assessed in the viral evaluation studies.

3. Regarding the in-process viral infectivity tests:

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

4. Regarding your viral control strategy:

- a. Please provide Q-PCR test results for all viruses that have been identified as a potential to infect patients. This includes HEV, EMCV, SVDV, Reo, Rota A influenza A and VSV.
- b. Please provide a calculation of estimated enveloped and non enveloped viruses per dose of API based on the limit of detection of the Q-PCR based assays from sufficient batches of the drug substance and discuss how your proposal provides an appropriate level of control for enveloped and non enveloped viruses, given the current estimate of the manufacturing process's ability to inactivate these viruses. Given the potential process capability of your manufacturing process, we believe that routinely monitoring by Q-PCR those viruses that potentially can infect humans and conducting infectivity testing of Q PCR positive batches is appropriate.
- c. Although you plan to (b)(4), we do not believe this information will be useful in mitigating the risk associated with the presence of infectious PPV because there does not appear to be a correlation between (b)(4) and infectivity. Please revise your specifications to include routine testing for PPV infectivity for all lots and provide a proposed acceptance criterion along with your justification for this proposal.
- d. You have detected by Q-PCR both PCV 1 and PCV 2 viral genomes. Your proposal to use PPV infectivity testing as a surrogate for PCV infectivity is not appropriate because these are completely unrelated viruses. Therefore, please establish a specification for infectious PCV 1 and PCV 2.

### APPENDIX 3: DP Deficiency Items – First Action

Deficiencies in Drug Product (from DMF Deficiency Letter sent to Eurand dated July 1, 2008; Master File #15681):

1. In regards to drug product release specification and acceptance criteria, we have the following comments:
  - a. Please provide acceptance criteria for the identification assay (b)(4) assay).
  - b. Please include testing for (b)(4) content, product-related substances and impurities (i.e. degradants) in your release program.
  - c. Please provide an acceptance criterion with a range for capsule weight in your release program.
  - d. Please provide the release test sampling plans.
2. In regards to your drug product stability program, we have the following recommendations:
  - a. Please include testing for (b)(4) content, product-related substances and impurities (i.e. degradants) in your stability program.
  - b. Please provide stability data with trend analysis on lots manufactured in 2006 and 2007.
3. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. Please develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.
4. Due to the potential inconsistencies of and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
5. You have not submitted sufficient information in the DMF to allow for the evaluation of your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing and establish and justify specifications for critical olive oil components.
6. Please provide the (b)(4) Assay method used in the (b)(4) step of manufacturing.
7. Please describe the (b)(4) process used in the (b)(4) step of manufacturing, including in-process controls and related acceptance criteria.
8. Please provide detailed information regarding the chemistry, manufacturing and controls for the hydromellose phthalate used for enteric coating of the minitabets.
9. Please provide a summary of the process validation program. Process validation should be performed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.

## APPENDIX 4: NDA Deficiency Items – First Action

Deficiencies from the Approvable Letter (NDA 22-222) dated July 1, 2008 are provided below:

### Chemistry, Manufacturing and Controls

1. We found that the Drug Master Files (DMFs) supporting your application (DMF (b) (4) DMF 15681) are deficient. Letters stating all deficiencies have been sent to the DMF holders. Please be advised that the approvability of your NDA depends on satisfactory responses from the DMF holders.
2. In addition, we have the following comments:
  - a. You have not provided real time stability data to support a 24-month expiry. Furthermore, you have reported several “Out Of Specification” (OOS) findings that do not support your proposed expiry dating. All methods used in support of expiry must be validated and should not be changed during the stability studies. The stability data contained in your application are sufficient to support a dating period of nine months for the drug product. ICH Q5C indicates that expiry dating of products in which the active components are proteins should be set using real time, real temperature stability data.
  - b. Provide stability data on drug product lots manufactured in 2006 and 2007. Please include trend analysis of all stability data with the 95% confidence interval. A commitment to investigate OOS or out of trend results in stability testing should be stated in the stability protocol.
  - c. Include tests for (b) (4) content, product-related substances, and impurities (i.e. degradants) in your drug product release and stability programs.
  - d. Due to the potential inconsistencies and reliance on USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
3. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. Please develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.
4. Due to the potential inconsistencies of and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.

5. You have not submitted sufficient information in the DMF to allow for the evaluation of your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing and establish and justify specifications for critical olive oil components.
6. Please provide the (b)(4) Assay method used in the (b)(4) step of manufacturing.
7. Please describe the (b)(4) process used in the (b)(4) step of manufacturing, including in-process controls and related acceptance criteria.
8. Please provide detailed information regarding the chemistry, manufacturing and controls for the hydromellose phthalate used for enteric coating of the minitables.
9. Please provide a summary of the process validation program. Process validation should be performed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.

## APPENDIX 5: DS Deficiency Items – Second Action

Deficiencies in Drug Substance - including Virology (from DMF Deficiency Letter sent to (b) (4) dated September 15, 2009; Master File # (b) (4))

- 1) In regard to your RP-HPLC assay used to monitor the purity of 1286, we have the following comments:
  - a. Please describe the method used to calculate the peak ratio.
  - b. You have established provisional acceptance criteria for the RP-HPLC assay. The acceptance criteria for some of the peaks are too wide, allowing for more than 100-fold variability. Please revise the acceptance criteria to reflect manufacturing experience and process capability.
  - c. Please include acceptance criteria for the additional peaks/peak groups that are currently excluded from your analysis.
- 2) In regard to your RP-HPLC identity assay, please provide acceptance criteria based on peak area rather than absorbance ratios.
- 3) The (b) (4) process of 1208 should be revalidated to include the (b) (4) time challenge. The procedures to validate each (b) (4) should be repeated three times.
- 4) You have established an in-process control for lipase activity target value, based on the source of the glands. However, no information was included in your submission. Please provide the target lipase activity value for glands used in the 1208 manufacturing process.
- 5) Provide the method validation and final report for the RP-HPLC assay used in release and stability testing.
- 6) Provide samples of your drug substance label.
- 7) Please provide the results of the forced degradation studies used to evaluate the suitability of the RP-HPLC assay for stability testing.
- 8) On page 47 of the 2008 annual update (Section 3.2.S.2) you refer to “finished product”. Please clarify what you define as “finished product”.
- 9) In your release testing program of drug substance 1208, establish acceptance criteria with upper and lower limits for peak areas for all peaks identified by RP-HPLC.
- 10) We recommend you expand your olive oil testing program to include monitoring for critical olive oil attributes. Please establish acceptance criteria for critical olive oil components (i.e. oleic acid) based on your historical testing results.
- 11) Please submit the following enzyme method validation study protocols and reports to the DMF: Lipase (b) (4), Protease (b) (4), and Amylase (b) (4)

- 12) Please identify an expiry or hold time for 1208 drug substance before (b) (4) and provide data supporting your proposal.
- 13) Due to past inconsistencies of the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
- 14) Please submit the results of the study conducted to demonstrate the equivalency of the (b) (4)
- 15) You have not provided a detailed description of the sanitizing/cleaning procedures in place to help prevent viral cross-contamination between different batches of drug substance. Please provide a detailed description of your sanitization program and provide an assessment of the ability of cleaning agents currently used in the facility to inactivate diverse viral agents. If the cleaning agents are inadequate to eliminate highly resistant viral species, please, provide a plan to implement appropriate cleaning agents to ensure inactivation of such viral agents to prevent cross contamination between different batches of drug substance. Include a description of any additional procedures in place with respect to equipment contamination with a virus that poses a risk to product quality.
- 16) Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1) to establish lot release specifications for the drug substance.
- 17) Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release.
- 18) Provide a calculation of estimated enveloped and non enveloped viruses per dose of API (NDA 22-222) based on the limit of detection of the Q-PCR assays from sufficient batches of the drug substance and discuss how your proposal provides an appropriate level of control for enveloped and non enveloped viruses, given the current estimate of the manufacturing process's ability to inactivate these viruses.
- 19) The sensitivity of the qPCR assays used to monitor for EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reovirus), Rota (Rota Virus), VSV (Vesicular Stomatitis Virus), and PTV (Porcine Teschovirus) viruses is in the range of (b) (4) genomes per gram. The sensitivity is suboptimal. Please provide plans to improve assay sensitivity.
- 20) Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
- 21) Revise your animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

- 22) Provide the following information regarding the handling and testing of the intact pancreas glands prior to (b) (4):
- a. Are the glands washed or processed in any way prior to (b) (4)
  - b. Are microbiological acceptance criteria in place for the pancreas glands?
- 23) Section 3.2.S.2.1.2.2 of DMF (b) (4) states that the maximum length of the pancreatin/pancrelipase manufacturing process is (b) (4). Please provide the following information regarding the manufacturing process:
- a. A justification for this extended processing time
  - b. The maximum storage time and storage temperature of the (b) (4) stored in (b) (4) drums
  - c. Data showing that the (b) (4) stored in the (b) (4) drums does not support microbial growth

## **APPENDIX 6: DP Deficiency Items – Second Action**

Deficiencies in Drug Product (from DMF Deficiency Letter sent to Eurand dated September 15, 2009; Master File #15681):

1. Data from release tests performed on encapsulated product.
2. Results of microbial limit testing performed on every lot manufactured. Include the results in your Certificate of Analyses.
3. In your release test sampling, the contents of capsules collected from different drums are mixed together. Revise your release test sampling to include the testing of individual capsules and provide the data collected using the revised sampling.
4. The release and stability acceptance criteria proposed for the RP-HPLC assay are not adequate. Establish and justify release and stability acceptance criteria for all peaks identified in the RP-HPLC chromatogram.
5. Revise acceptance criteria for moisture content to reflect process capability and historical results.
6. Data collected using the updated stability testing program and acceptance criteria provided in the DMF update.

## APPENDIX 7: NDA Deficiency Items – Second Action

Deficiencies from the Complete Response Letter (NDA 22-222) dated September 9, 2009 are provided below:

### PRODUCT QUALITY

1. The (b)(4) DMF (b)(4) and the EURAND DMF #15681 have been reviewed in support of NDA 022222 and found to contain deficiencies. Letters will be sent to (b)(4) and EURAND listing the deficiencies. (b)(4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when (b)(4) and EURAND have submitted the requested information.
2. Your annual stability data (Batches D070151C, D070151A, F070244B, F070244A, F070224D, F070224A, D070145B, C080114D, C080114C, D080118A, D080118C, D080151C, C080115A, D080119A) indicate that stability tests are performed before the product is packaged in its final container/closure system. Clarify if all stability studies you have performed were conducted on drug product prior to final packaging. Stability studies should be performed on packaged drug product using the final container/closure system.
3. Submit stability data collected using the updated stability program and acceptance criteria submitted in the NDA.
4. You have not provided a study that addressed the stability of the product once the final container is opened by the pharmacist or by the patient. Provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.
5. The stability data you have provided for the 12 count bottle only support a 12 month expiry. Revise your label accordingly, or provide additional data to support your requested dating period of 16 months.

### RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

6. As described in our letter dated May 20, 2009, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for TRADENAME (pancrelipase, USP) Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

We acknowledge the submission of your REMS documents on June 2, 2009. Once FDA finds the content of your REMS acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states

how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

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

“Dispense the accompanying Medication Guide to each patient.”

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

**NDA 022222**  
**PROPOSED REMS-AMENDMENT**

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

**LABELING**

7. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

## APPENDIX 8: DS Deficiency Items – Third Action

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

- 1) You have developed a Reversed Phase HPLC (RP-HPLC) assay to monitor product quality at release and during storage. For this assay, you propose an acceptance criterion based on the mean peak area  $\pm$  (b) (4) SD. Your proposed acceptance range is too wide and is not justified by your manufacturing history and current estimate of process capability. Please revise your acceptance criterion for the RP-HPLC assay to reflect manufacturing history and process capability, and include the revised acceptance criterion in your release and stability protocols.
- 2) In response to our request to establish an expiry or hold time for 1208 drug substance before (b) (4), and to provide data supporting the proposed expiry, you proposed a (b) (4) month retest date and a 24 month expiry. However, no data were provided in the submission to justify such limits. Please be aware that retest is generally not acceptable for protein products because protein products may undergo non-linear degradation. Therefore, expiry should be established based upon real time stability data. Please provide such data to support your proposed expiry date for the 1208 drug substance. Alternatively, you can set a hold time for (b) (4) 1208 that is supported by the real time stability data you currently have, and extend the hold time when additional data become available. Please be aware that when establishing the hold time for the (b) (4) material, you should provide data supporting the stability of drug substance taking into consideration the cumulative storage time of the (b) (4) and (b) (4) drug substance.
- 3) You have submitted enzyme assay validation protocols and results for both the (b) (4) and the (b) (4) testing sites. Please clarify whether both sites will be used to perform the release assays. If both sites will be used, please provide assay transfer protocols and results in support of the equivalency of the two sites.
- 4) You have provided updated stability data using the RP-HPLC assays for lots that are currently entered in your stability protocol. However, the RP-HPLC assay was performed only for limited time points. Please provide additional stability data, when available, to support the proposed shelf life.

## **APPENDIX 9: DP Deficiency Items – Third Action**

Deficiencies in Drug Product (from DMF Deficiency Letter sent to Eurand dated May 4, 2010; Master File #15681):

1. You have developed a Reversed Phase HPLC (RP-HPLC) assay to monitor product quality at release and during storage. For this assay, you propose an acceptance criterion based on the mean peak area  $\pm$  <sup>(b)</sup><sub>(4)</sub> SD. Your proposed acceptance range is too wide and is not justified by your manufacturing history and process capability. Please revise your acceptance criterion for RP-HPLC to reflect manufacturing history and process capability, and include the revised acceptance criterion in your release and stability protocols.
2. You have provided updated stability data using the RP-HPLC assays for lots that are currently entered in your stability protocol. However, the RP-HPLC assay was performed only for limited time points. Please provide additional stability data, when available, to support the proposed shelf life.

## APPENDIX 10: NDA Deficiency Items – Third Action

Deficiencies from the CR Letter (NDA 22-222) dated May 5, 2010 are provided below:

### PRODUCT QUALITY

1. The (b) (4) ( (b) (4) DMF # (b) (4) and the EURAND DMF #15681 have been reviewed in support of NDA 022222 and found to contain deficiencies. Letters have been sent to (b) (4) and EURAND listing the deficiencies. (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when (b) (4) and EURAND have submitted the requested information.
2. We noted a discrepancy in the description of the capsules printing between your NDA submission and the description provided in the package insert. Please amend your NDA submission to be consistent with the information provided in the package insert.

### RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

3. As described in our letter dated May 20, 2009, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Ultresa (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

We acknowledge receipt of your proposed REMS submitted on June 2, 2009 which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

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

**NDA 022222  
PROPOSED REMS-AMENDMENT**

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

### LABELING

4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

## APPENDIX 11: DS Microbiology Deficiency Items – Third Action

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

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

## **APPENDIX 12: NDA Deficiency Items – Fourth Action**

Deficiencies from the CR Letter (NDA 22-222) dated November 28, 2010 are provided below:

### **PRODUCT QUALITY**

The (b) (4) LLC ( (b) (4) DMF # (b) (4) has been reviewed in support of NDA 022222 and found to contain deficiencies. A letter dated October 27, 2010, was sent to (b) (4) listing several deficiencies regarding the drug substance manufacturing process. FDA conveyed additional information requests at a face-to-face meeting held on November 15, 2010, with you and representatives from (b) (4) should address all deficiencies by directly submitting information to their DMF, or, if the information was previously submitted, then by specific reference to the appropriate submissions. Please notify us when (b) (4) has submitted the requested information. Satisfactory resolution of the deficiencies identified is required before this application may be approved.

### **FACILITY INSPECTIONS**

During an inspection of a manufacturing facility referenced in this application, (b) (4) (b) (4) LLC ( (b) (4) conducted between (b) (4) (b) (4), the FDA investigator conveyed deficiencies to a representative of the facility. (b) (4) response dated (b) (4) (b) (4), addressing the deficiencies listed on FDA form 483 dated (b) (4) (b) (4), was not adequate. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

As described in our letter dated May 20, 2009, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Ultresa (pancrelipase) Delayed-Release Capsules to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of pancreatic enzyme products (PEPs), and the theoretical risk of transmission of viral disease to patients.

We acknowledge the submission of your proposed REMS on June 2, 2009, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS  
“**PROPOSED REMS-AMENDMENT for NDA 022222.**”

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

## APPENDIX 13: DS Deficiency Items – Fourth Action

Deficiencies in Drug Substance (from Letter sent to (b) (4) dated October 27, 2010; Master File # (b) (4))

1. Provide a list of all contract laboratories that will be used in support of manufacturing your products. Include the specific tests that will be performed by each laboratory, the company name, and address where testing is to be conducted. For each laboratory provide a point of contact including name, phone, fax, and email address.
2. For any contract laboratory used in support of manufacturing your products, provide a copy of the quality agreement between the contract laboratory and the associated manufacturing site.
3. For NDA 022222, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
4. For NDA 022542, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
5. For NDA (b) (4), provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
6. The establishment inspection report indicates that you have implemented a change in the drug substance intermediate storage container, from (b) (4) (b) (4) white drums to (b) (4) (b) (4) blue drums. Provide the results of studies conducted to demonstrate that the change in storage container will not adversely impact product quality. Specifically, submit the following information:
  - a. Extractable/leachable studies and risk analysis performed on the (b) (4) storage container.
  - b. Evaluation of the quality of pancrelipase manufactured using the (b) (4) containers.
  - c. Available stability data on lots of pancrelipase manufactured using the (b) (4) containers.
  - d. Since your process provides for re-use of the drug substance intermediate storage container, provide the results of validation studies performed to support re-use of the (b) (4) container.

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

7. Provide an update on efforts to reduce the bioburden on incoming pancreas glands.
8. Provide the microbial limits specification for pancreatin drug substance manufactured using the 1206 and 1208 processes.
9. Update the manufacturing procedures for the 1208 and 1206 processes with clearly defined time limits for each manufacturing step and the points at which samples for microbiological testing will be collected.
10. Update the information regarding microbiological monitoring of the (b) (4) with the following:
  - a. The bioburden alert and action levels from the (b) (4) manufactured using the 1206 and 1208 manufacturing processes.
  - b. A commitment to test the bioburden of the (b) (4) from each drum immediately prior to (b) (4)
11. Reaffirm your actions provided previously in the May 4, 2010 amendment to DMF (b) (4) (response to item 2) regarding exceeded microbiological alert and action levels.
12. Provide a commitment to clean all processing equipment between individual batches.
13. Section 3.2.S.7.1.2.4.1 in the August 12, 2010 submission lists the total aerobic microbial count (TAMC) limits for stability batches of drug substance at  $\leq$  (b) (4) CFU/g (1206) and  $\leq$  (b) (4) CFU/g (b) (4). The microbial limits for all pancrelipase stability batches should be at or below the levels established for release testing. Provide updated stability batch acceptance criteria for each of the pancreatin products.
14. As a condition of NDA approval:
  - a. Develop and implement a release test procedure that monitors for the presence of *Bacillus cereus* diarrheal enterotoxin in pancrelipase samples.
  - b. Provide a commitment to test each batch of drug substance for *Bacillus cereus* diarrheal enterotoxin prior to release.

**APPENDIX 14: Summary of Observations Cited in FDA Form 483 (issued to (b) (4) and to (b) (4) – Fourth Action**

(b) (4)

A summary of each of the observations cited in FDA Form 483 issued to (b) (4) is provided below.

(b) (4)

(b) (4)

A summary of each of the observations cited in FDA Form 483 issued to (b) (4) (contract testing laboratory for (b) (4)) is provided below.

(b) (4)



(b) (4)

## APPENDIX 15: Dosing Calculations - Children 1 to 10 Years Old

The table below is modified from the PMHS Consult Review by Elizabeth Durmowicz for Ultresa (dated May 12, 2010):

### Dosing Calculations for Girls, 1 To 10 Years Old<sup>1</sup>

Age (yrs)	Weight (kg)	Weight Based Dosing <sup>2</sup>	Recommended Starting Dose per Meal	Recommended Starting Dose per Snack (½ meal dose)
			Lipase Units	Lipase Units
1	9.5	1000 lipase units/kg per meal	9,500	4,750
2	12	“	12,000	6,000
3	14	“	14,000	7,000
4	16	500 lipase units/kg per meal	8,000	4,000
5	18	“	9,000	4,500
6	20	“	10,000	5,000
7	23	“	11,500	5,750
8	26	“	13,000	6,500
9	29	“	14,500	7,250
10	33	“	16,500	8,250

1. Girls' weights are based on the 50% weight for age and were chosen as girls typically weigh less than boys' of the same age.
2. Dosing calculations are based on the current weight-based dosing recommendations in the literature.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANIL K RAJPAL  
02/09/2012