CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-222Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of Safety Update Report

NDA#:	22, 222 (sequence# 0068)
Sponsor:	Axcan Pharma, Inc
Product:	Ultresa (pancrelipase)
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted:	September 1, 2011
PDUFA Date:	March 1, 2012
Date of Review:	December 16, 2011
Clinical Reviewer:	Marjorie F. Dannis, M.D.
Through:	Anil Rajpal, M.D.

Background

Ultresa (formerly known as Ultrase) is an orally administered porcine pancreatic enzyme preparation (PEP) that was previously indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It was available in the United States as a prescription drug from November 1991 until April 2010 when it was removed, as all marketed PEPs were required to have an approved NDA for continued marketing. Since Ultresa had never been approved under an NDA, it was no longer allowed to be marketed in the US. However, Ultresa is currently marketed under the trade name Ultrase MT in Canada, Argentina, Brazil and Chile.

The initial NDA was submitted on July 31, 2007. After several review cycles, most recently, on November 28, 2010, the Agency issued a Complete Response letter secondary to issues related to Facility Inspections and Product Quality. The complete response was submitted on September 1, 2011 and in accordance with 21 CFR 314.50(d)(5)(vi)(b), Axcan Pharma submitted a safety update with this complete response.

Safety Update

This safety update covers the period from May 5, 2010 to June 30, 2011.

Clinical Study

“Efficacy and safety of Ultrase MT12 in the control of steatorrhea in cystic fibrosis (CF) and pancreatic insufficient (PI) children aged 2 to 6 years old”

Study UMT12CF08-01 was a multicenter, open label, explorative phase 3b study. The primary objective of this study was to assess the efficacy of Ultrase MT12 in the control

of steatorrhea in CF children with PI. The secondary objectives were to assess the efficacy of Ultrase MT12 in the control of clinical signs and symptoms associated with malabsorption and to assess the tolerability of Ultrase MT12. Fifty-four cystic fibrosis children with PI, ages 2 to 6 years inclusively, from 15 centers in the USA were enrolled in the study, In total, forty-five subjects completed the study (five failed screening and four were withdrawn before completing the study). In the Safety Population (n = 48), the mean (SD) extent of exposure to Ultrase MT12 in the Treatment phase was 20.0 (3.5) days. All Treatment Emergent Adverse Events (TEAEs) in the Treatment phase are summarized below in Table 1.

Table 1: TEAEs by System Organ Class and Preferred Term for Study UMT12CF08-01, Safety Population N = 48)

System Organ Class Preferred Term	Study Phase Treatment Phase (Ultrase® MT12)	
	Number of Subjects with Event n (%)	Number of Events n
Treatment Emergent AEs	24 (50.0%)	49
Blood and lymphatic system disorders	1 (2.1%)	1
Lymphadenopathy	1 (2.1%)	1
Ear and labyrinth disorders	1 (2.1%)	1
Ear pain	1 (2.1%)	1
Gastrointestinal disorders	9 (18.8%)	17
Abdominal distension	1 (2.1%)	1
Abdominal pain	2 (4.2%)	2
Abdominal pain upper	2 (4.2%)	2
Constipation	3 (6.3%)	3
Diarrhoea	2 (4.2%)	2
Gastrooesophageal reflux disease	1 (2.1%)	1
Nausea	1 (2.1%)	1
Steatorrhoea	1 (2.1%)	1
Vomiting	4 (8.3%)	4
General disorders and administration site conditions	4 (8.3%)	4
Pyrexia	4 (8.3%)	4
Immune system disorders	1 (2.1%)	1
Seasonal allergy	1 (2.1%)	1
Infections and infestations	4 (8.3%)	4
Gastroenteritis viral	1 (2.1%)	1
Influenza	1 (2.1%)	1
Lobar pneumonia	1 (2.1%)	1
Nasopharyngitis	1 (2.1%)	1

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Table 1: TEAEs by System Organ Class and Preferred Term for Study UMT12CF08-01, Safety Population N = 48 (Cont'd)

System Organ Class Preferred Term	Study Phase Treatment Phase (Ultrase® MT12)	
	Number of Subjects with Event n (%)	Number of Events n
Investigations	4 (8.3%)	6
Faecal fat increased	2 (4.2%)	4
Forced expiratory volume decreased	1 (2.1%)	1
Weight decreased	1 (2.1%)	1
Metabolism and nutrition disorders	2 (4.2%)	2
Decreased appetite	2 (4.2%)	2
Nervous system disorders	1 (2.1%)	1
Headache	1 (2.1%)	1
Respiratory, thoracic and mediastinal disorders	8 (16.7%)	11
Cough	5 (10.4%)	5
Nasal congestion	4 (8.3%)	4
Rhinorrhoea	2 (4.2%)	2
Skin and subcutaneous tissue disorders	1 (2.1%)	1
Hyperhidrosis	1 (2.1%)	1

No deaths or serious adverse events occurred during this study. One TEAE, consisting of moderate constipation, led to discontinuation of a patient during the Treatment phase with Ultrase MT12. However, a reasonably possible relationship with the study drug was excluded by the Sponsor. A narrative for this patient is provided below.

- A three-year old patient was enrolled in this study on August 17, 2009 and started the first dose of study medication on August 31, 2009. A few days before the first dose of study medication (Ultrase MT12), this patient reported abdominal pain while he was on his usual enzyme treatment and this AE resolved spontaneously on the same day. A week and a half after starting the study medication, the subject started to complain again of abdominal pain on September 9, 2009 and an x-ray done on September 14, 2009 showed significant stool back up in his intestines. The investigator started him on Miralax and the subject was withdrawn from the study on September 14 due to need of using a prohibited medication. The investigator considered this AE as not related to the study medication.

Medical Reviewer's Comment:
This reviewer agrees with the Sponsor's conclusion stated above.

Conclusions

The Sponsor reports that due to significant differences in study design and patient population between Study UMT12CF08-01 and previously completed clinical studies on Ultrase, a combined safety database would be difficult to interpret, and therefore no integration was attempted. No significant changes were observed in the safety profile for Ultrase MT12 in this study compared to previous clinical experience; the common AEs

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were similar to those previously observed, and no serious or unexpected events occurred. The results of this trial do not significantly change the safety conclusions in the Ultrase NDA

Medical Reviewer's Comment:
This reviewer agrees with the Sponsor's conclusions as stated above.

Postmarketing
This section discusses the post-marketing experience of Ultrase recorded in the drug safety database maintained by Axcan Pharma Inc. and its subsidiaries. The drug safety database includes spontaneous cases from healthcare professionals and non-healthcare professionals as well as cases from scientific literature and regulatory authorities.

Adverse Events
Between May 5, 2010 and 30 and June 30, 2011, Axcan Pharma received six initial adverse event reports including a total of 23 adverse events. See Table 2 below. Five of these reports involved Ultrase and one involved an unspecified brand of pancrelipase.

Table 2: Adverse Events by System Organ Class received from May 5, 2010- June 30, 2011

SOC / Preferred Term	ULTRASE®	Pancrelipase unspecified	Total
Gastrointestinal disorders			
Abdominal pain	2	0	2
Diarrhoea	2	0	2
Nausea	1	0	1
Oral discomfort	1	0	1
Oral pain	1	0	1
Pancreatitis	0	1	1
Pancreatitis necrositing	0	1	1
Retching	1	0	1
Vomiting	1	0	1
General disorders and administration site conditions			
Concomitant disease aggravated	1	0	1
Drug ineffective for unapproved indication	1	0	1
Immune system disorders			
Hypersensitivity	1	0	1
Infections and infestations			
Post procedural infection	1	0	1
Investigations			
Hepatic enzyme increased	0	1	1
Pancreatic enzymes increased	1	0	1

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Table 2: Adverse Events by System Organ Class received from May 5, 2010 - June 30, 2011(Cont'd)

SOC / Preferred Term	ULTRASE®	Pancrelipase unspecified	Total
Musculoskeletal and connective tissue disorders			
Trismus	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer	1	0	1
Nervous system disorders			
Burning sensation	1	0	1
Headache	1	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1	0	1
Pleural effusion	0	1	1
Total	**19**	**4**	**23**

Two of the above adverse events reports were assessed as serious and are described below.

1. The first serious report was received from spontaneous notification and was not medically confirmed. It describes the occurrence of breast cancer, post-surgical infection and diarrhea in a 58-year-old patient treated with Ultrase MT20 capsules for PI. Concomitant medications included unspecified pain killers and natural thyroid supplements. No medical history was reported. The patient initiated a treatment with Ultrase MT20, one capsule per meal. She experienced diarrhea that got worse over time. Soon after, she received a breast cancer diagnosis. She underwent a mastectomy and was then hospitalized due to a post-surgical infection. At the hospital, she was switched from Ultrase MT20 to Creon. Subsequent to the treatment change, the diarrhea abated. The outcome for breast cancer and post surgical infection was not reported.

The Sponsor reports that considering the positive de-challenge manifested as the disappearance of diarrhea after removal of Ultrase, there is a reasonable possibility for a causal relationship between Ultrase and diarrhea. There is no reasonable possibility for a causal relationship between breast cancer and Ultrase because of the absence of a biological plausibility. In addition, there is no reasonable possibility for a causal relationship between post surgical infection and Ultrase because this event was a procedural complication.

2. The second serious report was retrieved from the literature [Verma *et al*, 2010] and describes the occurrence of commensal bacteria induced necrotizing pancreatitis, gallstone pancreatitis, pleural effusion and elevated alanine aminotransferase/ alkaline phosphatase levels in a 68-year-old patient treated with pancrelipase (formulation not reported) for an unknown indication. 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.

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On an unspecified date, the patient had an episode of gallstone pancreatitis which was complicated by pancreatic pseudocyst formation. Elective cholecystectomy was planned but not performed at that time due to the patient's unstable medical condition. Two months later, he presented to the reporter's hospital where a diagnosis of commensal bacteria induced necrotizing pancreatitis with fluid collection was made after a computerized tomogram (CT) of the abdomen/ pelvis that showed a pleural effusion, inflammation of the pancreas with prominent pseudocyst (with air-fluid levels in the tail of pancreas as well as a smaller air-filled fluid collection in the head of pancreas). CT guided drainage of pancreatic pseudocyst was performed and drained a purulent cloudy fluid which revealed beaded gram positive rods. Patient was treated with penicillin and trimethoprim/ sulfamethoxazole for Veillonella and Bifidobacterium infection.

The patient underwent surgery after 4 weeks and had an uneventful course with serial abdominal CT scans showing resolution of peripancreatic fluid collection and inflammation. Two weeks after discharge from a rehabilitation facility, the patient had resolution of his symptoms and was back to his usual state of health.

According to the Sponsor, there is no reasonable possibility for a causal relationship between pancrelipase and any of the adverse events due to the absence of biologic plausibility and the likelihood that the patient had been prescribed pancrelipase for the gallstone pancreatitis. (The start date of pancrelipase compared to the onset date of this event could not be confirmed). Furthermore, the other adverse events were most probably secondary to known complications of gallstone pancreatitis.

Medical Reviewer's Comment
This reviewer agrees with the Sponsor's assessment of the first SAE in that there is a reasonable possibility for a causal relationship between Ultrase and diarrhea. In addition, this reviewer agrees with the Sponsor's assessment and that there is no reasonable possibility for a causal relationship between breast cancer and Ultrase and no reasonable possibility for a causal relationship between post surgical infection and Ultrase.
Moreover, the limited adverse event data presented above are mostly consistent with the known adverse event profile of PEPs or are single incidences of one adverse event.

Patient exposure
During the period of May 1, 2010 to 30 to June 30, 2011, Ultrase MT Capsules were not distributed in the United States. Thus, an estimate of the patient exposure to Ultrase MT Capsules was calculated for the period of May 1, 2010 to 30 to June 30, 2011 from the number of product units distributed in Canada. Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

- The majority of patients taking Ultrase MT Capsules for the correction of steatorrhea are CF patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. Forty percent of the CF population is over 18 years of age.

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- The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the CFF show that between the ages of birth to 20 years, CF patients generally lie between the 20th and 40th percentile for weight.

- An average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC clinical growth charts for males and females between the ages of two and 20 years.[1]

- A starting dose of 500-1,000 USP lipase units/kg/meal (with titration to less than 2,500 lipase units/kg/meal) for pancreatic enzymes supplementation was recommended by the CFF, therefore, an average dose of 1,500 USP lipase units/kg/meal of Ultrase MT was assumed for calculation purposes.

- Patients would be consuming a total of four meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for Ultrase MT12 and Ultrase MT20 was calculated to be 23.6 capsules and 14.2 capsules, respectively.

Sales

Table 3 below presents unit sales information for Ultrase MT Capsules in Canada as well as the calculation of patient exposure. The estimate of the patient exposure in Canada is 34,120 patient-treatment-days assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of three meals and two snacks per day.

Table 3: Unit Sales of Ultrase MT Capsules (May 1, 2010 to 30-June 30, 2011) and Patient Exposure in Canada

	MT12 Btl 100 ct	MT20 Btl 100 ct
Total number of bottles	(b) (4)	
Total number of capsules		
Number of days of treatment		
Total number of patient-treatment-days	34,120	

[1] http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts htm#Clin%201

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Literature

A search of medical literature for the period of May 5, 2010 to 31 to June 31, 2011 was performed in Embase and Medline databases and retrieved the three relevant articles listed below.

- Konstan [2009 and 2010] present the results of Axcan's clinical trials UMT20CF07-01 and UMT12CF08-01 that are part of the NDA submission.

- Werlin and co-authors [2010] conducted a proof of concept trial to explain the reason of failure of pancreatic enzymes treatment to completely correct malabsorption and gastrointestinal symptoms in patients with CF. The aim of the study was to examine entire small intestine to search for evidence of inflammation by direct inspection of the mucosa of patients with CF without overt evidence of gastrointestinal disease using capsule endoscopy (CE).

The trial included 42 patients with CF ages 10 to 36 years. One patient was withdrawn from the study. Twenty-eight had pancreatic insufficiency (PI), and 13 were pancreatic sufficient (PS). All of the patients with (PI) were receiving pancreatic enzyme replacement therapy at the time of the study. The author used the fecal calprotectin test and wireless capsule enteroscopy (WCE) to quantify and localize intestinal inflammation, respectively, in patients with CF and relate these findings to clinical status. The findings on WCE showed varied pathological findings in the jejunum and ileum. Diffuse or localized small bowel lesions including villous blunting, edema, erythema, denuded mucosa, and mucosal breaks (erosions or ulcers) were observed throughout the jejunum and ileum in 26 of 41 (63%) patients. This study demonstrated a new observation, a high prevalence of small bowel injury in patients with CF, both patients with PI and those who were PS. The macroscopic appearance of the small intestine may be an integral part of the CF phenotype because it does not relate to the degree of pancreatic disease. In summary, the present proof-of-concept study suggested that there is a condition compatible with a "CF bowel" that may explain the persistence of malabsorption and gastrointestinal symptoms in patients with CF.

Summary/Conclusion

This report presented an update of post-marketing experience, scientific literature and study UMT12CF08-01. No new safety issues were identified during the covered period. The information presented in this safety update appears to be consistent with the previous safety profile of Ultrase MT and the known adverse event profile of PEPs.

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/s/

MARJORIE F DANNIS
12/20/2011

ANIL K RAJPAL
12/20/2011

MEMORANDUM

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

DATE: November 24, 2010

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules
Axcan Pharma US, Inc.

Summary

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

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Ultresa (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. Before this application may be approved, the following must be satisfactorily completed: 1) submission of adequate information supporting a change in the drug substance intermediate storage containers, 2) resolution of ongoing discussions involving proposed modifications to in-process microbial controls for the drug substance manufacturing process and the feasibility of *Bacillus cereus* diarrheal enterotoxin testing, 3) resolution of deficiencies identified during inspection of the drug substance manufacturing facility, and 4) resolution of discussions regarding the product label, REMS, and postmarketing study requirements and commitments.

Dosing

Ultresa (pancrelipase) Delayed-Release Capsules are dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Ultresa should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences.

Ultresa use in pediatric patients is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Since the lowest available dosage strength will be 13,800 USP units of lipase, dosing with Ultresa will not be possible for the lowest weight infants. If approved, product labeling will specify dosing recommendations for children 1-4 years of age weighing 14 kg or greater, and for patients 4 years of age and older weighing 28 kg or greater. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

Ultresa (pancrelipase) Delayed-Release Capsules are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Ultresa, is pancrelipase, which consists

[1] Ultresa has been marketed in the US as "Ultrase" since 1991. The to-be-marketed product, Ultresa, is the same formulation as the previously marketed formulation.

of the enzymes lipase, amylase and protease, as specified in the US Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. Thus, if approved, the **Dosage and Administration** section of the Ultresa label will state that "Ultresa is not interchangeable with any other pancrelipase product."

Regulatory History[2]

Axcan Pharma US, Inc. (formerly Axcan Scandipharm, Inc.) submitted NDA 022222 on September 28, 2007, received on October 1, 2007, and was granted a priority review. A major amendment extended the review clock to July 1, 2008. Concurrent with review of this NDA, FDA reviewed submissions to DMF # (b) (4) from the drug substance manufacturer, (b) (4) ((b) (4) and to DMF #15681 from the drug product manufacturer, Eurand S.p.A, which support this NDA. FDA issued an approvable letter on July 1, 2008 due to unresolved CMC deficiencies.

A complete response was submitted on April 7, 2009, and a proposed REMS on June 2, 2009. Inspection of (b) (4) in (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 and involved (b) (4). Based on these findings, the Office of Compliance recommended withholding NDA approval. FDA issued a complete response letter on September 9, 2009.

An inspection of the Eurand manufacturing facility performed in October 2009 was satisfactory. Axcan Pharma US, Inc. submitted a complete response on November 5, 2009 triggering a third review cycle.

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

In a review dated April 30, 2010, the Division of Microbiology, CFSAN, did not agree that the positive assay results could represent false positive results. The review further stated that if the drug substance lots were "…made with any level of consistency and the batches are homogeneous, it seems that 7/7 samples would have tested positive…" The Office of Compliance again recommended withholding NDA approval and planned to conduct another pre-approval inspection of this facility to assess the adequacy of additional, yet-to-be-implemented, microbiologic controls of the drug substance manufacturing process. FDA issued a third complete response letter on May 5, 2010. In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.[3]

On May 28, 2010, Axcan Pharma US, Inc. submitted a complete response triggering a fourth review cycle. Inspections were conducted of (b) (4) ((b) (4) and (b) (4) ((b) (4)) and FDA form 483s were issued to both firms. There were (b) (4) observations cited for (b) (4) including (b) (4)). (b) (4) There were (b) (4) observations cited for (b) (4) one (b) (4)

[2] Additional details may be found in the review by Dr. Daniel Shames dated July 1, 2008, and my previous reviews dated September 9, 2009 and May 5, 2010.
[3] See memo dated October 25, 2010, from Reginald Bennett, Jennifer Hait, and Sandra Tallent.

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

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, discussed the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Ultresa (pancrelipase) Delayed-Release Capsules. Recommendations from this Advisory Committee included informing patients of this theoretical risk and monitoring for potential viral transmission to users of these products (see below).

Chemistry, Manufacturing and Controls (CMC) Considerations

Axcan Pharma US, Inc. intends to market three capsule strengths containing 13,800, 20,700, and 23,000 USP units of lipase, respectively. The capsules contain identical small enteric-coated minitablets of (b) (4) pancreatic enzymes (lipase, amylase and pancrease). The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5. Stability studies of the minitablets mixed in acidic foods (e.g., applesauce, yogurt) support the use of these foods to administer the tablets.

Drug substance ((b) (4) The drug substance, DS 1286, is (b) (4) Several CMC deficiencies involving the drug substance have been identified and previously conveyed to (b) (4) At this time, the Division of Therapeutic Proteins has determined that deficiencies involving the capacity of the manufacturing process to clear viruses and monitor viral load can be addressed as postmarketing commitments and do not preclude approval of the NDA. At the most recent inspection of (b) (4) FDA noted the use of (b) (4) blue drums for drug substance intermediate storage.[7] Given that drug substance (b) (4), extractable and leachable studies, evaluation of product quality, stability data, and validation studies to support re-use of the containers are needed. These information requests were conveyed to (b) (4) on October 27, 2010. Axcan Pharma US, Inc. and (b) (4) response received on November 9, 2010, will be reviewed in depth in the next review cycle.

Bulk drug product (Eurand). Several CMC deficiencies involving the bulk drug product have been identified and previously communicated to Eurand. At this time, there are no remaining deficiencies.

Packaged finished product (Axcan Pharma US, Inc). Several CMC deficiencies involving the packaged finished product have been identified and previously conveyed to Axcan Pharma US, Inc. These have now been adequately addressed.

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[4] (b) (4) was cited for not adequately investigating a complaint dated October 9, 2008, regardin (b) (4)

[5] (b) (4) has been used for release testing and historical testing for BDE in 726 samples since April 13, 2010.

[6] In contrast, the (b) (4)

[7] (b) (4) did not notify the NDA applicant of this manufacturing change or submit any information to support the change for FDA review.

Microbiology Concerns

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

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

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

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

At the conclusion of this meeting Axcan Pharma US, Inc. and (b) (4) agreed to submit 1) their current proposal for TAMC testing and arguments why it will prevent BDE formation during manufacturing, 2) results of all efforts to validate a BDE test method in the pancreatin matrix, 3) information that BDE is (b) (4) present in the pancreatin matrix, 4) information regarding changes made in the ports used for sampling pancreatin during the manufacturing process, and 5) information about the pancreatin product made under the previous manufacturing process that is still on the market and what they intend to do regarding these products. Responses from Axcan Pharma US, Inc. and (b) (4) submitted on November 18 and 22, 2010, respectively, will be reviewed in depth in the next review cycle.

Clinical Pharmacology

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

Efficacy

As with other PEP manufacturers, Axcan Pharma US, Inc. was requested to perform at least one controlled clinical trial with Ultresa to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.[8] Axcan Pharma US, Inc. conducted one double-blind, placebo-controlled crossover trial in 31 patients, aged 8-37 years (14 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Ultresa or placebo for 6-7 days, followed by crossover to the alternate treatment for an additional 6-7 days. The mean Ultresa dose during the controlled treatment periods was 6,270 lipase units/kg of body weight per day. All patients consumed a high fat diet. Ultresa treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ($p<0.0001$).

Safety

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

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of PEPs, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. Doses greater than 2,500 lipase units/kg of body weight per meal (or > 10,000 lipase units/kg of body weight per day) should be used with caution. Patients receiving doses higher than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range. If approved, a Medication Guide will be required as part of a REMS for Ultresa that will inform patients of this risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study in Ultresa users to assess the incidence of and potential risk factors for developing fibrosing colonopathy.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Ultresa is not retained in the mouth. Ultresa should not be crushed or chewed since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

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

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

[8] See http://www.fda.gov/cder/guidance/6275fnl htm

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

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

Tradename Review

On June 10, 2009, the Division of Medication Error Prevention and Analysis (DMEPA) informed Axcan Pharma US, Inc. that the tradenames "Ultrase MT-12", "Ultrase MT-18", and "Ultrase MT-20" are not acceptable. First, the proposed suffixes, MT-12, MT-18, and MT-20, are ambiguous in their meaning and vulnerable to misinterpretation. Second, the last three letters of the proposed proprietary name Ultrase contain the US Adopted Name (USAN) stem "-ase". The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. Therefore, USAN stems should not be incorporated into proprietary names. On July 7, 2009, the applicant submitted a different proprietary name for consideration. DMEPA informed the applicant on October 5, 2009, that the proposed tradename "Ultresa" was acceptable.

Pediatric Considerations

Pediatric Use. If approved, the **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Ultresa were demonstrated. In addition, the label will state that "The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience."

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

At the time of approval, FDA will determine the ages of pediatric patients with cystic fibrosis for which Axcan Pharma US, Inc., has fulfilled the pediatric study requirement. FDA will waive 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 below 1 month of age, so there would not be enough eligible patients in this age range to study.

At the time of approval, FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Postmarketing Requirements under 505(o)

As described in the complete response letter dated September 9, 2009, in accordance with section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that, if this application is approved, Axcan Pharma US, Inc. will be required to conduct the following studies to assess a known serious risk of fibrosing colonopathy and the unexpected risk of transmission of viral disease to patients taking Ultresa (pancrelipase) Delayed-Release Capsules:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultresa in the US and to assess potential risk factors for the event.

2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Ultresa.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

As described in our letter of 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 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.

Axcan Pharma US, Inc.'s proposed REMS, submitted on June 2, 2009, contains a Medication Guide and a timetable for submission of assessments of the REMS. Comments on the proposed Medication Guide from DGP and the Division of Risk Management were conveyed to the applicant on August 5, 2010. Axcan largely accepted these comments, with some additional editorial revisions.

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

/s/

JULIE G BEITZ
11/24/2010

Cross-Discipline Team Leader Review

Date	November 24, 2010
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-222
Applicant	Axcan Pharma US, Inc.
Date of Submission	May 28, 2010
PDUFA Goal Date	November 28, 2010
Proprietary Name / Established (USAN) names	Ultresa® pancrelipase
Dosage forms / Strength	Ultresa® (pancrelipase) delayed release-capsules for oral administration, in USP units ▪ Ultresa 13,800 lipase/27,600 protease/27,600 amylase ▪ Ultresa 20,700 lipase/41,400 protease/41,400 amylase ▪ Ultresa 23,000 lipase/46,000 protease/46,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Complete Response (CR) under 21 CFR 314

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1. Introduction

A Complete Response (CR) Letter was sent by the Division on May 5, 2010. This resubmission, received May 28, 2010, is a complete response to that letter, and represents the fourth 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, and third 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 ([redacted] (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.

No clinical deficiencies were identified in any of the review cycles. The initial submission included results from a clinical study using the To be Marketed Product (TbMP): pivotal study (UMT20CF05-01; CF-01; randomized double-blind cross-over study; n=31). The second submission, third submission, and the current submission contain clinical study safety updates. It should be noted that the TbMP is the same formulation as the unapproved Commercially Marketed Product (CMP).

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

2. Background

2.1 Clinical Background

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

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause. Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

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

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

<u>Approved PEPs</u>: 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.

<u>Unapproved PEPs</u>: 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;

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

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

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

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

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

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

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

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

2.2.2 Regulatory History of 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
July 2008	Approvable Action (first action)
September 2008	Meeting with the Sponsor to discuss items in the Division's Approvable Letter
April 2009	Class II Resubmission#
September 2009	Complete Response Action (second action)
November 2009	Class II Resubmission#
May 2010	Complete Response Action (third action)
May 2010	Meeting with the Sponsor to discuss items in the Division's CR Letter
May 2010	Class II Resubmission#

*IND 41387; #Complete Response to the Action Letter

It should also be noted that Ultresa was commercially available in the US from 1991 to earlier this year (see Section 2.2.1); it was marketed under the name "Ultrase." The CMP formulation that was on the market from 2003 to earlier this year 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

Correspondence that was cited by this reviewer consisted 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)

2.3 Current Submission

The NDA resubmission was received on May 28, 2010. It was classified as a six-month resubmission with a PDUFA deadline of November 28, 2010.

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 Ali Niak, dated November 10, 2010
(2) CMC Reviews from Division of Therapeutic Proteins (DTP):
  (a) Final Product Release and Packaging Reviews (filed under NDA 22-222)
    - Primary Review by Wei Guo, dated September 24, 2010
    - Secondary Review by Emanuela Lacana, dated November 23, 2010
  (b) Drug Product Review (filed under DMF 15681)
    - Primary Review by Wei Guo, dated September 24, 2010
  (c) Drug Substance Reviews (filed under DMF (b) (4)
    - Primary Review of Non-Viral Issues by Wei Guo (entered by Emanuela Lacana on behalf of Wei Guo), dated October 13, 2010
(3) Microbiology Reviews and Memos from New Drug Microbiology Staff (NDMS)
  (a) Reviews and Memo by Stephen Langille (filed under NDA 22-222):
    - Review dated June 30, 2010
    - Memo dated May 26, 2010
    - Review dated November 24, 2010
  (b) Review by Stephen Langille (filed under DMF (b) (4)
    - Review dated June 9, 2010
(4) Division of Risk Management (DRISK) Review by Steve Morin dated August 26, 2010
(5) DTP Carton and Container Label Reviews by Kimberly Rains, dated August 4, 2010, and August 11, 2010

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, and third review cycles, dated July 1, 2008, September 9, 2009, and May 5, 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 Final Product Release and Packaging (NDA 22-222) Review by Wei Guo dated September 24, 2010, the Drug Product (DMF 15681) Review by Wei Guo dated September 24, 2010, the Drug Substance Non-Viral Issues (DMF (b) (4) Review by Wei Guo dated October 13, 2010, the Microbiology Review (DMF (b) (4) by Stephen Langille dated June 9, 2010, the Microbiology Review (NDA 22-222) by Stephen Langille dated June 30, 2010, the Microbiology Memo (NDA 22-222) by Stephen Langille dated May 26, 2010, the Microbiology Review (NDA 22-222) by Stephen Langille dated November 24, 2010, and the CMC Secondary (Summary) Review (NDA 22-222) by Emanuela Lacana dated November 23, 2010 for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (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) The glands are (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b) (4) (b) (4) (b) (4) and (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) ((b) (4) and (b) (4) steps. To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

Overview of Drug Product (DP): The DP is manufactured by Eurand, the drug product Drug Master File (DMF) holder (DMF #15681), in a process that entail (b) (4) 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 minitablets that are 2.0 mm in diameter. A stability study with the minitablets mixed in foods (i.e., applesauce, pudding, and yogurt) was conducted to support the use of various foods to administer the minitablets (see Section 5 Clinical Pharmacology).

Overview of Final Product Release and Packaging: Axcan Pharma US, Inc. is responsible for the final DP release and final 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 (b) (4), 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, (b) (4) initiated an evaluation of the (b) (4) (b) (4) and (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 (b) (4) 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 [redacted] (b) (4)), and [redacted] (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 [redacted] (b) (4) [redacted] (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 [redacted] (b) (4) were related to (see final wording of Items #1 to #19 in Deficiency Letter to [redacted] (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, [redacted] (b) (4) content, microbial limits), storage conditions, and expiration date; (3) process data for DS 1208 (a primary drug substance) and DS 1286 ([redacted] (b) (4) (4) rejected batches may not be reworked or reprocessed; (5) in-process lipase activity and microbial limits acceptance criteria; (6) [redacted] (b) (4) [redacted] (b) (4) characterization study; (7) DS characterization for amylase; (8) DS 1286 release testing ; (9) specification for [redacted] (b) (4) content and impurities for release testing; (10) tightening of protease and amylase activity acceptance criteria; (11) [redacted] (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) [redacted] (b) (4) assay method used in the [redacted] (b) (4) step of manufacturing; (7) description of the [redacted] (b) (4) process for the [redacted] (b) (4) step of manufacturing; (8) information regarding the CMC for hypromellose phthalate used for the enteric coating of the minitablets; (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) (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 can be addressed as postmarketing commitments (PMC's). (The PMC's recommended by the DS Viral Issues reviewer were provided in the CDTL review from the third review cycle and are shown in Appendix 8 of this CDTL review.)

PMC's will be planned for negotiation with the Applicant should Ultresa receive an Approval action during a subsequent review cycle (see also Section 13.6).

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 9): (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 10): (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 11): (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 12): (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 Current Review Cycle

In the current 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. (The reader is referred to the Drug Substance Non-Viral Issues Review dated October 13, 2010, the Drug Product Review dated September 24, 2010, the Final Product Release and Packaging Review dated September 24, 2010, the Microbiology Reviews dated June 9, 2010, and June 30, 2010, the Microbiology Memo dated May 26, 2010, and CMC Secondary (Summary) Review dated November 23, 2010.)

3.4.1 DS Viral Issues (Current Cycle)

A DS Viral Issues Review was not conducted during the current 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 Section 3.3.1 of this CDTL review; see also Appendix 8 of this CDTL review for a listing of the PMC's recommended by the DS Viral Issues reviewer in the previous cycle.) PMC's will be planned for negotiation with the Applicant should Ultresa receive an Approval action during a subsequent review cycle (see also Section 13.6).

3.4.2 DS Non-Viral Issues (Current Cycle)

The DS Non-Viral Issues reviewer noted that each of the deficiencies identified in the previous cycle was adequately addressed; the secondary CMC reviewer identified additional deficiency items. (See Drug Substance Non-Viral Issues Review by Wei Guo dated October 13, 2010, and Secondary Review by Emanuela Lacana dated November 23, 2010 for complete information.)

<u>Response to Deficiency Items #1 to #4</u>: A summary of the DS Non-Viral Issues reviewer's assessment of the adequacy of (b) (4) response to Items #1 through #4 in the Letter to (b) (4) dated May 4, 2010 (see Appendix 9) is presented below.

(1) <u>RP-HPLC assay acceptance criteria in release and stability protocols</u>. This item was adequately addressed as the firm narrowed the acceptance criteria specifications from ± (b) (4) SD to ± (b) (4) SD; in addition, the firm also set specifications for lower limits of peaks (b) (4) and (b) (4) to (b) (4) and of lower limit of peak (b) (4) to (b) (4).

(2) <u>Real time stability data to support a 24-month expiry for the 1208 DS</u>. This item was adequately addressed as the firm provided 12 lots real time stability data, tested at 0, 3, 6,

9, 12, 18, 24, and 36 months to support the expiry of 36 months for 1208. The DS Non-Viral Issues Reviewer noted that all data were within the current acceptance range except for the Total Aerobic Microbial counts of one lot (which was > (b) (4) cfu/g at time=0 and > (b) (4) cfu/g at time = 12 months); the DS Non-Viral Issues Reviewer pointed out that at the time of testing, the acceptance range was NMT (b) (4) cfu/g. The DS Non-Viral Issues Reviewer also noted that further testing of TAMC of that lot were all below acceptance limit of (b) (4) cfu/g. The DS Non-Viral Issues Reviewer commented that the Microbiology Reviewer determined that the microbial tests and results were acceptable.

(3) Clarification of testing site(s) for performance of release assays. This item was adequately addressed as the firm clarified that all enzyme assay testing for release of final API batches will be performed by (b) (4)

(4) Stability data to support the proposed shelf-life. This item was adequately addressed as the firm committed to send the data when available.

Additional Deficiency Items: The additional deficiency items below are taken from the secondary (summary) review by Emanuela Lacana. (See Review by Emanuela Lacana dated November 23, 2010, for complete information.)

(1) During inspection of (b) (4) inspectors noted that changes to the drug substance intermediate container were introduced in the process, and the DMF holder was cited for lack of extractable leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported, however (b) (4) did not provide validation data or extractable/leachable studies for the new container. (Dr. Lacana noted that this issue was discovered after the primary review was completed and for this reason is not discussed in Wei Guo's review.) See **Item #6** in the Deficiency Letter sent to (b) (4) on October 27, 2010 (in Section 13.1.2 of this CDTL review).

(2) Both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase from (b) (4) for the presence of Bacillus cereus diarrheal enterotoxin and detected the toxin in several samples. (b) (4) claims that the results are false positive and that the false positive results are due to matrix interference. However, the DMF holder has provided no data to support this contention. See **Items #7 to #14** in the Deficiency Letter sent to (b) (4) on October 27, 2010 (in Section 13.1.2 of this CDTL review).

3.4.3 DP Issues (Current Cycle)

The DP reviewer noted that each of the deficiencies identified in the previous cycle were adequately addressed. The DP Reviewer identified three issues that could be addressed as postmarketing commitments (PMC's). (See Drug Product Review by Wei Guo dated September 24, 2010 for complete information.)

Response to Deficiency Items #1 to #2: A summary of the DP reviewer's assessment of the adequacy of Eurand's response to Items #1 through #2 in the Letter to Eurand dated May 4, 2010 (see Appendix 10) is presented below.

(1) Revised RP-HPLC assay acceptance criteria to reflect manufacturing history and process capability. This item was adequately addressed. The firm narrowed the acceptance criteria specifications from ± (b) (4) SD to ± (b) (4) SD; in addition, the firm also set specifications for lower limits of peaks (b) (4) and (b) (4) to (b) (4) and of lower limit of peak (b) (4) to (b) (4). The DP Reviewer noted that this is consistent with the specifications proposed by the DS manufacturer.

(2) Additional stability data to support the proposed shelf life. This item was adequately addressed as the firm has initiated the annual stability protocol as they had committed to the Agency. The DP Reviewer noted that the RP-HPLC test will be implemented using the current acceptance criteria (Mean ± (b) (4) SD), and that stability data of up to 3 months are provided. The DP Reviewer commented that the data provided were all within specifications.

Postmarketing Commitments: DP items to be communicated to Eurand (taken from Dr. Guo's review) as postmarketing commitments (PMC's) are provided below.

PMC #1: Evaluate stability of drug product manufactured using drug substance at the end of the shelf-life.

PMC #2: Revise release and stability specifications after 30 lots of drug product have been manufactured.

PMC #3: Include accelerated and/or stressed stability conditions in the annual stability protocol.

PMC's will be planned for negotiation with the Applicant should Ultresa receive an Approval action during a subsequent review cycle (see also Section 13.6).

3.4.4 Final Product Release and Packaging Issues (Current Cycle)

The Final Product Release and Packaging reviewer noted that the deficiency item identified in the previous cycle was adequately addressed. (See Final Product Release and Packaging Review by Wei Guo dated September 24, 2010 for complete information.)

Response to Deficiency Item #2: A summary of the Final Product Release and Packaging reviewer's assessment of the adequacy of Axcan's response to Item #2 in the CR Letter to the Applicant dated May 5, 2010 (see Appendix 11) is presented below.

(2) A discrepancy in the description of the capsules printing between the NDA submission and the description provided in the package insert. This item was adequately addressed as the Applicant has updated the printing on the capsule to be consistent with the description provided in the package insert (i.e., "13,800UL", "20700UL", and 23000UL" for the respective dosage strength formulations and "AXCA" are printed on the capsule body).

3.4.5 Microbiology Issues (Current Cycle)

The Microbiology Reviewer deemed the responses to each of the deficiency items in the letter sent to (b) (4) May 3, 2010 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) have been adequately addressed (see Section 13.1.2 of this CDTL Review). See Microbiology Review by Stephen Langille dated June 9, 2010 (filed under Master File # (b) (4) and Addendum dated November 24, 2010 (filed under NDA 22-222) for complete information.

Response to Deficiency Items #1 to #6 (in May 3, 2010 letter): A summary of the Microbiology reviewer's assessment of the adequacy of (b) (4) response to Items #1 through #6 in the Letter to (b) (4) dated May 3, 2010 (see Appendix 12) is presented below.

(1) Justification for in-process holding times (especially prior to "(b) (4) step"). (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) provided the processing and holding times and conditions for the 1206 and 1208 manufacturing processes.

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

(3) Explanation for wide range of TAMC prior to (b) (4) (for 1206 lots) and corrective actions. (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. (b) (4) stated that the wide range of TAMC is due to the sampling port located downstream of the (b) (4) and that the new sample port will be located to allow the sample to be withdrawn directly from the (b) (4) The following corrective actions were provided to ensure acceptable bioburden levels prior to the addition of (b) (4) (a) removal of the (b) (4)" for the 1206 process (see item #4 below); (b) addition of an in-process specification for the (b) (4) samples for the 1206 and 1208 process; and (c) use o (b) (4) The Microbiology Reviewer

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

(4) Rationale for selection of one of two 1206 activation processes [redacted] (b) (4)). [redacted] (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. [redacted] (b) (4) agreed to cease production using the [redacted] (b) (4) for the 1206 manufacturing process, and provided a revised 1206 manufacturing protocol.

(5) Request to provide the maximum storage time for the [redacted] (b) (4) [redacted] (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer. [redacted] (b) (4) stated that the maximum storage time for the 1208 process is no more than [redacted] (b) (4), and provided a summary of the microbiological studies to support the proposed [redacted] (b) (4) hold time. The Microbiology Reviewer commented that although a maximum holding time of [redacted] (b) (4) is not considered ideal, the [redacted] (b) (4) is stored in the presence of the [redacted] (b) (4) [redacted] (b) (4) and is unlikely to support microbial growth; he further noted that the [redacted] (b) (4) will be tested for TAMC prior to [redacted] (b) (4) and that the action level is no more than [redacted] (b) (4) CFU TAMC/g.

(6) Commitment to test Bacillus cereus enterotoxin prior to release including description of methods and validation. [redacted] (b) (4) response to each of the parts of this item was deemed satisfactory by the Microbiology Reviewer. (a) [redacted] (b) (4) stated in an amendment dated June 6, 2010, that the Bacillus cereus enterotoxin test will be a finished active pharmaceutical ingredient (API) release test for the 1206 and 1208 product. (b) A [redacted] (b) (4) algorithm for enterotoxin testing was provided in the June 6, 2010 amendment. The initial test will be done using the [redacted] (b) (4) BDE test. [redacted] (b) (4) [redacted] (b) (4) states that this test algorithm was implemented due to the high incidence of false positive results normally obtained using the [redacted] (b) (4) tests. The Microbiology Reviewer noted that the proposed BDE testing algorithm was judged to be acceptable by food safety experts from CFSAN. The Microbiology Reviewer further noted that as of June 6, 2010, [redacted] (b) (4) have not been validated to test for the presence of the BDE toxin. Therefore, it was agreed upon in a meeting with Axcan held May 20, 2010 (that included members of both Axcan and [redacted] (b) (4) that the [redacted] (b) (4) will be used as the release test until the [redacted] (b) (4) tests have been validated and the validation studies submitted to the FDA (see Response to Question 15 in Memo by Stephen Langille dated May 26, 2010 filed under NDA 22-222; also see Meeting Minutes dated June 18,

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

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

3.4.6 Facility Inspections (Current 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."

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

(b) (4)

An overview 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)

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

3.5 Final Recommendation

A Complete Response Action is the final recommendation by CMC.

Deficiency items to be communicated to the Applicant (NDA 22-222) and to the drug substance DMF holder (# (b) (4) are provided in Sections 13.1.1 and 13.1.2, respectively.

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[6], given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Ultresa clinical development 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:

- Indications and Usage section of Highlights: "Pancreatic enzyme preparation digestant" is recommended as the established pharmacologic class.
- 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

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

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."

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

4.2 Second Review Cycle

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

4.3 Third Review Cycle

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

4.4 Current Review Cycle

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

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

4.5 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline provided the labeling revisions described above are made.

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 minitablets in Ultresa Capsules is designed to dissolve at pH ≥ 5.5 which allows delivery of the enzymes to the duodenum. However, it was shown in the *in vitro* stability study that the minitablets were stable in chocolate pudding (approximate 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., minitablets 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 100^0C 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 37^0C.
- 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 minitablet 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 minitablets can only be mixed with acidic food (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.

Since Ultresa was not recommended for Approval during the second review cycle, labeling changes were not negotiated with the Applicant.

5.3 Third Review Cycle

There were no new clinical pharmacology data in the resubmission, and no additional review of clinical pharmacology data was performed in the third review cycle.

5.4 Current Review Cycle

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

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

5.5 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology discipline provided the labeling revisions described above are made.

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; CF-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 (Pivotal Study; Study CF-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

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
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	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-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 ≤40%),
- moderately-affected (>40 and ≤80%), and
- mildly-affected (>80%).

The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of ≤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 ≥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 is not 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 Review Cycle

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

7.3 Third Review Cycle

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

7.4 Current Review Cycle

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

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

7.5 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, and the Clinical Reviews of Safety Updates by Ali Niak, dated September 9, 2009, March 9, 2010, April 30, 2010, and November 10, 2010 for complete information.

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

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

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

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

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

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

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.

- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g., pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.

- Irritation to Oral Mucosa: Disruption of the protective enteric coating, and early release of the enzymes may lead to the irritation of the oral mucosa as well as loss of enzyme activity.

The theoretical risk of viral transmission is summarized below:

- Theoretical Risk of Viral Transmission: There is a concern that because PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[10,11] (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 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 Review Cycle

The reader is referred to the Clinical Review of Safety Update by Ali Niak, dated September 9, 2009 for complete information.

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

In the second review cycle, 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 review cycle safety update.

A summary of the Clinical Review of Safety Update for the second review cycle can be found in the second review cycle CDTL Review dated September 9, 2009.

8.3 Third Review Cycle

The reader is referred to the Clinical Reviews of Safety Updates by Ali Niak, dated March 9, 2010 and April 30, 2010 for complete information.

In the third review cycle, the AE profile of Ultresa as described in the clinical study updates 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 third review cycle safety updates.

A summary of the Clinical Reviews of Safety Updates for the third review cycle can be found in the third review cycle CDTL Review dated May 5, 2010.

8.4 Current Review Cycle

The reader is referred to the Clinical Review of Safety Update by Ali Niak, dated November 10, 2010 for complete information.

Dr. Niak 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. Niak notes that based on US unit sales of Ultrase® MT Capsules during the reporting period (February 1, 2010, to May 4, 2010), patient exposure was estimated to be approximately 1,072,705 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 30th percentile); weight was selected based on age and weight data in the Cystic Fibrosis Foundation (CFF) Registry. It should be noted that US sales of Ultrase® MT Capsules constitute the greatest percentage globally (more than (b)(4)%) although Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile and Canada).

For Ultrase® MT, a total of 10 case reports of adverse events were received. No serious adverse event was received during the reporting period. For Ultrase® MT, there were only

single occurrences of the following adverse events: upper abdominal pain, flatulence, nausea, decreased drug effect, ineffective drug, peripheral edema, rash, and skin irritation.

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 Pancreaze).

Clinical Study Update: No clinical studies were completed during the period from February 1, 2010, to May 4, 2010. A safety update was provided for Study UMT20CF08-01, an ongoing study of CF patients aged 2 to 6 years old. The Applicant stated that the adverse events assessed as related to the study drug by the investigator were gastrointestinal in nature and were consistent with the previously known safety profile of the product, and that the clinical study report is under preparation.

Literature Update: The Applicant conducted a search of the medical literature for the period from February 1, 2010, to May 4, 2010. The Applicant stated that the literature search did not provide any new relevant safety information pertaining to Ultrase® MT or other formulations of pancreatic enzyme preparations.

8.5 Final Recommendation

Should Ultresa receive an Approval action during a subsequent review cycle, a Risk Evaluation and Mitigation Strategy (REMS) is recommended to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients (see Section 13.1 Recommended Regulatory Action, and see Section 13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements).

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Previous (Third) Review Cycle:

During the course of the review in the previous (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.

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.

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 two 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 ber 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 ber 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 13: 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.

Current Review Cycle:

In the current (fourth) review cycle, it was determined that it would not be necessary to present the application again to the Pediatric Research Committee (PeRC). The proposed labeling changes from the previous review cycle will be planned for negotiation with the Applicant should Ultresa receive an Approval action during a subsequent review cycle.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. 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 4. 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	Protocol violations: (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. Overall assessment: The data from this site can be used in support of the NDA.
Site 03 Steven Strausbaugh, MD Cleveland, OH	Six	Minor protocol violations: Two patients enrolled before results of fecal elastase results available; results later found to be within the protocol requirement. Overall assessment: The data from this site can be used in support of the NDA.

Information in the table above is taken from the CTDL 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 will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010.

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

11.4 Facility Inspections

During recent inspections of the [redacted] (b) (4) ([redacted] (b) (4) manufacturing facility for this application and of [redacted] (b) (4) (contract testing laboratory for [redacted] (b) (4) the field investigator conveyed deficiencies to the representative of the facilities; based on the Establishment Evaluation System (EES) report, there are "Withhold" recommendations from the Office of Compliance for both [redacted] (b) (4) and for [redacted] (b) (4) Satisfactory resolution of these deficiencies is required before this application may be approved. (See

also Sections 3.3.6 and 3.4.6.) (b) (4)

12. Labeling

12.1 Proprietary name

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 previous review cycle, no trade name had been agreed upon with the Applicant.

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.

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).]

Current Review Cycle:

There was no additional discussion of the proprietary name in the current review cycle. The proprietary name will be re-reviewed should Ultresa receive an Approval action during a subsequent review cycle. As per the Proprietary Name Granted Letter (dated October 5, 2009), the proposed proprietary name Ultresa will be re-reviewed 90 days prior to the approval of the NDA.

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

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

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

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The Primary CMC Reviewer (of Final Product Release and Packaging, of Drug Product, and of Non-Viral Drug Substance Issues) and the Secondary CMC Reviewer recommend this NDA for CR Action; all of the deficiency items are drug substance deficiencies and were communicated to the drug substance DMF Holder, (b) (4) (DMF (b) (4) in a separate letter dated October 27, 2010.

The Microbiology Reviewer concluded that this NDA can not be recommended for approval until the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) have been adequately addressed.

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

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

13.1.1 CR Letter to Axcan Pharma US, Inc. (NDA 22-222)

PRODUCT QUALITY

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

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 (SPL) 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.

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

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

1. Provide a list of all contract laboratories that will be used in support of manufacturing your products. Include the specific tests that will be performed by each laboratory, the company name, and address where testing is to be conducted. For each laboratory provide a point of contact including name, phone, fax, and email address.

2. For any contract laboratory used in support of manufacturing your products, provide a copy of the quality agreement between the contract laboratory and the associated manufacturing site.

3. For NDA 022222, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.

4. For NDA (b) (4), 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 [redacted] (b) (4) with the following:
    a. The bioburden alert and action levels from the [redacted] (b) (4) manufactured using the 1206 and 1208 manufacturing processes.
    b. A commitment to test the bioburden of the [redacted] (b) (4) from each drum immediately prior to [redacted] (b) (4)

11. Reaffirm your actions provided previously in the May 4, 2010 amendment to DMF [redacted] (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 [redacted] (b) (4) (1206) and ≤ [redacted] (b) (4)/g (1252). The microbial limits for all pancrelipase stability batches should be at or below the levels established for release testing. Provide updated stability batch acceptance criteria for each of the pancreatin products.

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

13.2 Risk Benefit Assessment

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

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

See Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since Ultresa is not recommended for Approval during this review cycle, recommendations for postmarketing pediatric requirements such as development of an age appropriate formulation will be made should Ultresa receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

> As described in our letter dated September 9, 2009, we have determined that if this application is approved, you will be required to conduct postmarketing studies for Ultresa (pancrelipase) Delayed-Release Capsules to assess a known serious risk of fibrosing colonopathy and an unexpected serious risk of transmission of viral disease to patients taking Ultresa (pancrelipase) Delayed-Release Capsules.
>
> 1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultresa (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.
> 2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Ultresa (pancrelipase) Delayed-Release Capsules.
>
> Any additional specific details for these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.
>
> If you complete one or both of these studies prior to re-submitting your application, you may include the final report(s) and relevant data sets in your Complete Response submission to facilitate review of the information.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

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

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995[12]) 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[13] 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[14] states:

> "A 1995 consensus conference on the use of pancreatic-enzyme supplements sponsored by the U.S. Cystic Fibrosis Foundation recommended that the daily dose of pancreatic enzymes for most patients remain below 2500 units of lipase per kilogram

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

per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations."

APPENDIX 2: 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) (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 [redacted] (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 [redacted] (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 minitablets.

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 minitablets.

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 [redacted] (b) (4):

    a. Are the glands washed or processed in any way prior to [redacted] (b) (4)?

    b. Are microbiological acceptance criteria in place for the pancreas glands?

23) Section 3.2.S.2.1.2.2 of DMF [redacted] (b) (4) states that the maximum length of the pancreatin/pancrelipase manufacturing process is [redacted] (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 [redacted] (b) (4) stored in [redacted] (b) (4) drums

    c. Data showing that the [redacted] (b) (4) stored in the [redacted] (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 [redacted] (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: PMC's Recommended by DS Viral Issues Reviewer - Third Cycle

[The Postmarketing Commitments (PMC's) recommended by the DS Viral Issues Reviewer in the third review cycle shown below are taken from the CDTL Review for the third review cycle.]

PMC #1: Submit the final study reports of the cleaning agents effectiveness for viral inactivation for protocols # 09-VV-17-020 & 09-VV-12-121 to the FDA. (Final Report Submission date to be determined as per review.)

PMC #2: Submit the validation report for the PCV1 (Porcine Circovirus 1) infectivity release assay to the FDA. (Final Report Submission by December 2010 as per review.)

PMC #3: Establish lot release specifications for the PCV1 infectivity assay. (Final Report Submission by June 2011 as per review.)

PMC #4: Establish lot release specifications for the PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) infectivity assay. (Final Report Submission by October 2010 as per review.)

PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide better assurance that released drug substance will not contain EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reo Virus), Rota (Rota Virus), PTV (Porcine Teschovirus) viruses. Revise the assays, and submit assay validation data, together with acceptance criteria. (Final Report Submission date to be determined as per review.)

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

APPENDIX 9: 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 ± (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 10: 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 ± (b)(4) 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 11: NDA Deficiency Items – Third Action

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

PRODUCT QUALITY

1. The [redacted] (b) (4) ([redacted] (b) (4) DMF # [redacted] (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 [redacted] (b) (4) and EURAND listing the deficiencies. [redacted] (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when [redacted] (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 12: 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) (b) (4) step" are of particular importance since most of the microbial proliferation occurs during that stage of the manufacturing process.

2. Provide the following information regarding in-process microbial alert and action levels for the 1206 and 1208 Pancreatin manufacturing processes:
   a. The total aerobic microbial count (TAMC) alert and action levels for (b) (4) samples collected following (b) (4) but immediately before the addition of (b) (4) to the (b) (4). TAMC alert and action levels should be commensurate with those obtained from (b) (4) gland samples as reported in the 16 April 2010 submission to the agency.
   b. TAMC alert and action levels for samples of the (b) (4) collected immediately prior to (b) (4)
   c. A summary of the actions taken when alert and action levels are exceeded

3. Provide an explanation for the wide range of TAMC prior to the addition of (b) (4) for 1206 pancreatin lots (< (b) (4) CFU/g in 39 lots as compared to > (b) (4) /g in 11 lots) in the data provided in attachment 5 of the 16 April 2010 submission. Provide a list of corrective actions to be taken to ensure that acceptable bioburden levels are achieved prior to the addition of (b) (4) to the (b) (4)

4. According to the manufacturing procedure listed on pages 790-791 of volume 24.14 of DMF (b) (4) the 1206 (b) (4) process can take place for (b) (4) Explain the rationale for determining which process to use and correlate the TAMC counts obtained in the 1206 process samples (attachment 5 of the 16-April-2010 document) with the holding times and temperatures used for each batch.

5. Step f) (1) of the 1208 process description states that (b) (4) ". Provide the maximum storage time for the 1208 (b) (4) prior to (b) (4)

6. Provide the following information regarding testing for the diarrheal form of *Bacillus cereus* enterotoxin:
   a. A commitment to test each batch of Pancreatin drug substance for *Bacillus cereus* enterotoxin prior to release
   b. A description of the *Bacillus cereus* enterotoxin test method, the validation procedure, and a summary of the supporting validation data.

APPENDIX 13: Dosing Calculations - Children 1 to 10 Years Old

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

Dosing Calculations for Girls, 1 To 10 Years Old[1]

Age (yrs)	**Weight** (kg)	**Weight Based Dosing[2]**	**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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/s/

ANIL K RAJPAL
11/24/2010

Medical Officer's Review of Safety Update Report

NDA #:	22-222
Applicant:	Axcan Pharma US, Inc.
Product:	ULTRASE® MT / ULTRASE
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted/Received:	May 6, 2010
PDUFA Date:	November 24, 2010
Date of Review:	November 10, 2010
Clinical Reviewer:	Ali Niak, M.D., Medical Officer, DGP
Through:	Anil Rajpal, M.D., Acting Team Leader, DGP

BACKGROUND

ULTRASE® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been available on the United States (US) market since November 1991. Axcan Pharma Inc. has been marketing ULTRASE® MT Capsules since August 1999 in the US. In addition, ULTRASE® is currently marketed in Canada, Argentina, Brazil and Chile.

SAFETY UPDATE

A Safety Update was submitted by the Applicant on May 6, 2010. The Safety Update covered the period from February 1, 2010, to May 4, 2010, for post-marketing information, and from February 1, 2010, to April 28, 2010, for clinical study information. Pertinent findings from the Safety Update are presented below.

Completed Clinical Study Update

No clinical studies were completed during the period from February 1, 2010, to May 4, 2010.

Ongoing Clinical Study Update

Study UMT20CF08-01 is a multicenter, open-label, Phase IIIb trial of ULTRASE® MT12 (enteric coated with HP-55, the formulation currently on the market) in the control of steatorrhea in cystic fibrosis children with pancreatic insufficiency. A total of 54 patients between 2 to 6 years of age enrolled in the study, of which, 5 of them failed the screening procedures and 4 were withdrawn before completing the study. In total, 45 patients completed the study. Initial drafts of the protocol were submitted to IND 41,387 on April 29, 2008 and November 11, 2008. Subsequently, the protocol was amended to include clarifications on the high fat diet, to better define the "optimized dose" of lipase to be used, and to provide an objective criteria that will be used to determine this "optimized dose." This was done in order to not exceed the current Cystic Fibrosis Foundation guideline for maximum dosing to minimize the risk of fibrosing colonopathy. The protocol was formally submitted to IND 41,387 on March 24, 2009.

The enrolment of patients started on April 29, 2009, and was completed on September 25, 2009. The last subject completed the study on November 4, 2009. The database was closed on January 12, 2010.

The adverse events assessed as related to the study drug by the investigator were gastrointestinal in nature and were consistent with the previously known safety profile of the product. The clinical study report is under preparation.

Post-Marketing Information

Between February 1, 2010, and May 4, 2010, Axcan Pharma Inc. and its subsidiaries received 10 initial and no (0) follow-up adverse event reports including a total of 23 adverse events. From these reports, 5 involved ULTRASE®, 4 involved VIOKASE®, and one involved PANZYTRAT®. No serious adverse event was received during the reporting period.

The table below presents the adverse events of all three products recorded in the database classified by body system [MedDRA standard organ system classification scheme (SOC)] during the period from February 1, 2010, to May 4, 2010.

Table 1. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from February 1, 2010, to May 4, 2010.

SOC / Preferred Term	Ultrase®	Viokase®	Panzytrat®	Total
Gastrointestinal disorders				
Abdominal pain upper	1	0	0	1
Diarrhoea	0	1	0	1
Flatulence	1	0	0	1
Nausea	1	1	0	2
Oral discomfort	0	1	0	1
Oral pain	0	1	0	1
Retching	0	1	0	1
Vomiting	0	1	0	1
General disorders and administration site conditions				
Concomitant disease aggravated	0	1	0	1
Drug effect decreased	1	0	0	1
Drug ineffective	1	0	1	2
Oedema peripheral	1	1	0	2
Therapeutic response decreased	0	1	0	1
Immune system disorders				
Hypersensitivity	0	1	0	1
Musculoskeletal and connective tissue disorders				
Trismus	0	1	0	1
Nervous system disorders				
Burning sensation	0	1	0	1
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	0	1	0	1
Skin and subcutaneous tissue disorders				
Rash	1	0	0	1
Rash pruritic	0	1	0	1
Skin irritation	1	0	0	1
Total	**8**	**14**	**1**	**23**

(Table above is taken from Page 6 of the Safety Update for NDA 22-222 dated May 6, 2010.)

For ULTRASE, there were only single occurrences of the following adverse events: upper abdominal pain, flatulence, nausea, decreased drug effect, ineffective drug, peripheral edema, rash, and skin irritation. Please refer to the above table.

The limited adverse event data presented above are consistent with the known adverse event profile of pancreatic enzyme products (PEPs).

Cumulative Sales and Exposure

An estimate of the patient exposure to ULTRASE® MT Capsules was calculated for the period of February 1, 2010, to April 28, 2010 from the number of product units distributed in the United States.

Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1. The majority of patients taking ULTRASE Capsules for the correction of steatorrhea are cystic fibrosis patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally are between the 20th and 40th percentile for weight.
2. Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts (Set 1) for males and females between the ages of 2-20 years. (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201). A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supplementation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from ULTRASE Capsule supplementation was assumed for calculation purposes.
3. It was assumed that patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for ULTRASE MT12, ULTRASE MT18, and ULTRASE MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. The table below lists unit sales information for ULTRASE MT Capsules in the United States as well as the calculation of patient-exposure-years from February 1, 2010, to April 28, 2010.

Table 2. Unit Sales of ULTRASE® MT Capsules (February 1, 2010, to April 28, 2010) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment				
Total number of patient-treatment-days	1,072,705			

(Table above is taken from Page 8 of the NDA 22-222 Safety Update dated May 6, 2010.)

The estimate of the patient exposure during the 3-month reported period is 1,072,705 patient-treatment-days assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

LITERATURE UPDATE

No new relevant safety information pertaining to ULTRASE or other formulations of pancreatic enzyme preparations was noted in a search of medical literature for the period from February 1, 2010, to May 4, 2010, as noted in the Safety Update Report dated May 6, 2010.

SUMMARY/CONCLUSION

The limited safety information submitted in the Safety Update Report covering the period from February 1, 2010, to May 4, 2010, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE capsules during the reporting period were (b) (4) capsules. Patient exposure to ULTRASE was estimated to be 1,072,705 "patient-treatment-days."

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

/s/

ALI NIAK
11/10/2010

ANIL K RAJPAL
11/10/2010
I concur with Dr. Niak.

MEMORANDUM

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

DATE: May 5, 2010

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules
Axcan Pharma US, Inc.

Summary

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

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Ultresa (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. Before this application may be approved, the following must be satisfactorily addressed or resolved: 1) the identified chemistry, manufacturing, and controls (CMC) deficiencies for the drug substance and bulk drug product (to be addressed by the respective DMF holders), and for the packaged finished product (to be addressed by Axcan Pharma US, Inc.), 2) the identified microbiological deficiencies involving the drug substance manufacturing process; 3) re-inspection of the drug substance manufacturing facility to assess the adequacy of additional, yet-to-be-implemented, microbiologic controls, and 4) discussions regarding the product label, REMS, and postmarketing study requirements and commitments.

Dosing

Ultresa (pancrelipase) Delayed-Release Capsules are dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Ultresa should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences.

Ultresa use in pediatric patients is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Since the lowest available dosage strength will be 13,800 USP units of lipase, dosing with Ultresa will not be possible for the lowest weight infants. If approved, product labeling will specify dosing recommendations for children 1-4 years of age weighing 14 kg or greater, and for patients 4 years of age and older weighing 28 kg or greater. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

Ultresa (pancrelipase) Delayed-Release Capsules are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Ultresa, is pancrelipase, which consists

[1] Ultresa has been marketed in the US as "Ultrase" since 1991. The currently marketed formulation has been available since 2003. The to-be-marketed product, Ultresa, is the same formulation as the currently marketed formulation.

of the enzymes lipase, amylase and protease, as specified in the US Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. Thus, if approved, the **Dosage and Administration** section of the Ultresa label will state that "Ultresa is not interchangeable with any other pancrelipase product."

Regulatory History[2]

Axcan Pharma US, Inc. (formerly Axcan Scandipharm, Inc.) submitted NDA 022222 on September 28, 2007, received on October 1, 2007, and was granted a priority review. A major amendment extended the review clock to July 1, 2008. Concurrent with review of this NDA, FDA reviewed submissions to DMF # (b) (4) from the drug substance manufacturer, (b) (4) (b) (4) and to DMF #15681 from the drug product manufacturer, Eurand S.p.A, which support this NDA. FDA issued an approvable letter on July 1, 2008 due to unresolved CMC deficiencies.

A complete response was submitted on April 7, 2009, and a proposed REMS on June 2, 2009. Inspection of (b) (4) in (b) (4) identified (b) (4) deficiencies that were described in a 483 and involved (b) (4) . Based on these findings, the Office of Compliance recommended withholding NDA approval. FDA issued a complete response letter on September 9, 2009.

An inspection of the Eurand manufacturing facility performed in October 2009 was satisfactory. Axcan Pharma US, Inc. submitted a complete response on November 5, 2009 triggering a third review cycle.

A re-inspection of the (b) (4) facility was performed in (b) (4) and identified (b) deficiencies. During that inspection, FDA obtained and conducted microbiological testing on samples from three drug substance lots; 4 out of 5 test samples tested positive for *E. coli*. An outside laboratory retained by (b) (4) tested the same lots using the same assay that FDA had used and all were found to be negative. In January 2010, FDA collected additional samples from seven lots; analysis showed that none of the samples tested positive for *E. coli*, but all seven contained low levels of *Bacillus cereus* and one of the seven tested positive for *B. cereus* diarrheal enterotoxin. (b) (4) has retained (b) (4) to retest these lots. Using a variation of the test method previously used by FDA, they found that all seven lots tested negative for enterotoxin suggesting that the positive finding in the single lot may have been a false positive. In a review dated April 30, 2010, the Division of Microbiology, CFSAN, did not agree that the result was a false positive. The review further stated that if the drug substance lots were "…made with any level of consistency and the batches are homogeneous, it seems that 7/7 samples would have tested positive…" The Office of Compliance continues to recommend withholding NDA approval and plans to conduct another pre-approval inspection of this facility to assess the adequacy of additional, yet-to-be-implemented, microbiologic controls of the drug substance manufacturing process.

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, discussed the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Ultresa (pancrelipase) Delayed-Release Capsules. Recommendations from this Advisory Committee included informing patients of this theoretical risk and monitoring for potential viral transmission to users of these products (see below).

Chemistry, Manufacturing and Controls (CMC) Considerations

Axcan Pharma US, Inc. intends to market three capsule strengths containing 13,800, 20,700, and 23,000 USP units of lipase, respectively. The capsules contain identical small enteric-coated minitablets of (b) (4) pancreatic enzymes (lipase, amylase and pancrease). The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5. Stability studies of the minitablets mixed in acidic foods (e.g., applesauce, yogurt) support the use of these foods to administer the tablets.

[2] Additional details may be found in the review by Dr. Daniel Shames dated July 1, 2008, and my previous review dated September 9, 2009.

Drug substance ((b) (4) The drug substance, DS 1286, is a (b) (4) DS 1208.[3] Several CMC deficiencies involving the drug substance have been identified and previously conveyed to (b) (4) At this time, the Division of Therapeutic Proteins has determined that deficiencies involving the capacity of the manufacturing process to clear viruses and monitor viral load can be addressed as postmarketing commitments and do not preclude approval of the NDA. Several additional deficiencies remain which do preclude approval. These involve acceptance criteria for drug substance release and stability protocols, the need for additional data supporting expiry and stability, and information regarding the equivalence of two sites that may be performing release assays. Drug substance deficiencies involving chemistry, manufacturing, and controls were conveyed directly to (b) (4) on May 4, 2010.

Bulk drug product (Eurand). Several CMC deficiencies involving the bulk drug product have been identified and previously communicated to Eurand. At this time, there are remaining deficiencies that Eurand will have to address involving acceptance criteria for drug product release and stability protocols and the need for additional stability data. Bulk drug product deficiencies involving chemistry, manufacturing, and controls were conveyed directly to Eurand on May 4, 2010.

Packaged finished product (Axcan Pharma US, Inc). Several CMC deficiencies involving the packaged finished product have been identified and previously conveyed to Axcan Pharma US, Inc. These have now been adequately addressed. However, a new deficiency has been identified, namely, that the applicant should clarify the discrepancies between the descriptions of the capsule printing between the NDA submission and the proposed package insert. This deficiency will be conveyed to Axcan Pharma US, Inc. in the complete response letter.

Microbiology Concerns

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

(b) (4) will therefore need to implement additional microbiologic controls of the drug substance manufacturing process, and provide 1) a justification for all in-process holding times associated with manufacture of the drug substance, 2) the maximum storage time for the (b) (4) prior to (b) (4) 3) information on total aerobic microbial count alert and action levels at particular points in the manufacturing process, 4) a commitment to test each batch of drug substance for *B. cereus* diarrheal enterotoxin prior to release, and 5) a description of the *B. cereus* diarrheal enterotoxin test method, the validation procedure, and a summary of the supporting validation data. These deficiencies were conveyed directly to (b) (4) on May 3, 2010.

Clinical Pharmacology

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

Efficacy

As with other PEP manufacturers, Axcan Pharma US, Inc., was requested to perform at least one controlled clinical trial with Ultresa to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug*

[3] In contrast, (b) (4) .

Products – Submitting NDAs.[4] Axcan Pharma US, Inc. conducted one double-blind, placebo-controlled crossover trial in 31 patients, aged 8-37 years (14 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Ultresa or placebo for 6-7 days, followed by crossover to the alternate treatment for an additional 6-7 days. The mean Ultresa dose during the controlled treatment periods was 6,270 lipase units/kg of body weight per day. All patients consumed a high fat diet. Ultresa treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ($p<0.0001$).

Safety

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

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of pancreatic enzyme products, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution. Patients receiving doses higher than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range. If approved, a Medication Guide will be required as part of a REMS for Ultresa that will inform patients of this risk.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Ultresa is not retained in the mouth. Ultresa should not be crushed or chewed since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

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

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

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

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

[4] See http://www.fda.gov/cder/guidance/6275fnl htm

Tradename Review

On June 10, 2009, the Division of Medication Error Prevention and Analysis (DMEPA) informed Axcan Pharma US, Inc. that the tradenames "Ultrase MT-12", "Ultrase MT-18", and "Ultrase MT-20" are not acceptable. First, the proposed suffixes, MT-12, MT-18, and MT-20, are ambiguous in their meaning and vulnerable to misinterpretation. Second, the last three letters of the proposed proprietary name Ultrase contains the US Adopted Name (USAN) stem "-ase". The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. Therefore, USAN stems should not be incorporated into proprietary names. On July 7, 2009, the applicant submitted a different proprietary name for consideration. DMEPA informed the applicant on October 5, 2009, that the proposed tradename "Ultresa" was acceptable.

Pediatric Considerations

Pediatric Use. If approved, the **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Ultresa were demonstrated. In addition, the label will state that "The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience."

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

At the time of approval, FDA will determine the ages of pediatric patients with cystic fibrosis for which Axcan Pharma US, Inc., has fulfilled the pediatric study requirement. FDA will waive 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 below 1 month of age, so there would not be enough eligible patients in this age range to study.

At the time of approval, FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Postmarketing Requirements under 505(o)

As described in the complete response letter dated September 9, 2009, in accordance with section 505(o)(3) of the FDCA, we have determined that, if this application is approved, Axcan Pharma US, Inc. will be required to conduct the following studies to assess a known serious risk of fibrosing colonopathy and the unexpected risk of transmission of viral disease to patients taking Ultresa (pancrelipase) Delayed-Release Capsules:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultresa in the US and to assess potential risk factors for the event.

2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Ultresa.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

As described in our letter of 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 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.

Axcan Pharma US, Inc.'s proposed REMS, submitted on June 2, 2009, contains a Medication Guide and a timetable for submission of assessments of the REMS. FDA's review of the proposed REMS has been deferred to the next review cycle.

_____

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

JULIE G BEITZ
05/05/2010

Cross-Discipline Team Leader Review

Date	May 5, 2010
From	Anil Rajpal, MD, Acting Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-222
Applicant	Axcan Pharma US, Inc.
Date of Submission	November 5, 2009
PDUFA Goal Date	May 5, 2010
Proprietary Name / Established (USAN) names	Ultresa® pancrelipase
Dosage forms / Strength	Ultresa® (pancrelipase) delayed release-capsules for oral administration, in USP units ▪ Ultresa 13,800 lipase/27,600 protease/27,600 amylase ▪ Ultresa 20,700 lipase/41,400 protease/41,400 amylase ▪ Ultresa 23,000 lipase/46,000 protease/46,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Complete Response (CR) under 21 CFR 314

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1. Introduction

A Complete Response (CR) Letter was sent by the Division on September 9, 2009. This resubmission, received November 5, 2009, is a complete response to that letter, and represents the third 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 both the first and second 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 (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).

No clinical deficiencies were identified in either the first or the second review cycles. The initial submission included results from a clinical study using the To be Marketed Product (TbMP): pivotal study (UMT20CF05-01; CF-01; randomized double-blind cross-over study; n=31). The second submission and the current submission contain clinical study safety updates. It should be noted that the TbMP is the same formulation as the unapproved Commercially Marketed Product (CMP).

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

2. Background

2.1 Clinical Background

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. The most common cause of EPI in children is

Cystic Fibrosis (CF); the most common cause of EPI in adults is chronic pancreatitis (CP). There are many other causes, such as pancreatectomy.

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause. Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

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

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

Approved PEPs: 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.

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

Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products

Year	Federal Register Notices
April 1995	Notice of Final Rule: All PEPs must obtain FDA approval under NDA in order to remain on the market.
April 2004	Notice of Requirement for NDA Approval: All PEPs must obtain NDA approval within the next four years (deadline April 28, 2008)
October 2007	Notice of Extension: FDA would use enforcement discretion for the PEPs. In order to continue marketing their products, manufacturers must have: ▪ open IND by April 28, 2008, ▪ NDA submitted by April 28, 2009, and ▪ approved NDA by April 28, 2010.

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

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

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

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

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

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

2.2.2 Regulatory History of 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
July 2008	Approvable Action (first action)
September 2008	Meeting with the Sponsor to discuss items in the Division's Approvable Letter
April 2009	Class II Resubmission#
September 2009	Complete Response Action (second action)
November 2009	Class II Resubmission#

*IND 41387; #Complete Response to the Action Letter

It should also be noted that Ultresa has been commercially available in the US since 1991; it is marketed under the name "Ultrase." The current CMP formulation has been on the market since 2003. The current CMP 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

Correspondence that was cited by this reviewer consisted 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)

2.3 Current Submission

The NDA resubmission was received on November 5, 2009. It was classified as a six-month resubmission with a PDUFA deadline of May 5, 2010.

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 Reviews of Safety Updates by Ali Niak, dated March 16, 2010, and dated April 30, 2010
(2) CMC Reviews from Division of Therapeutic Proteins (DTP):
   (a) Final Product Release and Packaging Issues Review by Wei Guo, dated April 30, 2010 (filed under NDA 22-222)
   (b) Drug Product Review by Wei Guo, dated April 30, 2010 (filed under DMF 15681)
   (c) Drug Substance Non-Viral Issues Review by Wei Guo, dated April 30, 2010 (filed under DMF (b) (4)
   (d) Drug Substance Viral Issues Review by Howard Anderson (DTP), dated April 28, 2010 (filed under NDA 22-222)
(3) Microbiology Reviews by Stephen Langille, dated March 29, 2010 (filed under NDA 22-222), and dated April 12, 2010 (filed under DMF (b) (4)
(4) Division of Medication Error and Prevention Analysis (DMEPA) Label and Labeling Review by Denise Baugh dated April 15, 2010
(5) Division of Drug Marketing, Advertising, and Communications (DDMAC) Labeling Memo by Kathleen Klemm dated March 9, 2010
(6) Study Endpoints and Labeling Development (SEALD) Labeling Review by Jeannie Delasko dated March 4, 2010

Additional documents that are relevant to the current review are the following:

- Medical Necessity Determination (for unapproved PEPs; filed under 22523) by Marjorie Dannis dated February 22, 2010
- Health Hazard Evaluation (for PEPs manufactured from (b) (4) drug substance; filed under NDA's 22222, (b) (4), and (b) (4) by Anil Rajpal dated February 23, 2010

Correspondence cited by this reviewer consisted of the following:

- Proprietary Name Granted Letter sent to Axcan Pharma US, Inc. (c/o CanReg, Inc.) dated October 5, 2009 (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 Review dated July 1, 2008, for the initial review cycle, the CDTL Review dated September 9, 2009, for the second review cycle, 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 Final Product Release and Packaging (NDA 22-222) Review by Wei Guo dated April 30, 2010, the Drug Product (DMF 15681) Review by Wei Guo dated April 30, 2010, the Drug Substance Non-Viral Issues (DMF (b) (4) Review by Wei Guo dated April 30, 2010, the Drug Substance Viral Issues (NDA 22-222) Review by Howard Anderson dated April 28, 2010, the Microbiology Review (DMF (b) (4) by Stephen Langille dated April 12, 2010, and the Microbiology Review (NDA 22-222) by Stephen Langille dated March 30, 2010, for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (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) The glands are (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b) (4), (b) (4) (b) (4) and (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) ((b) (4) and (b) (4) steps. To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

Overview of Drug Product (DP): The DP is manufactured by Eurand, the drug product Drug Master File (DMF) holder (DMF #15681), in a process that entail (b) (4) Ultresa capsules come in three strengths, Ultresa MT12, MT18, and MT20, containing 13,800, 20,700 and 23,000 USP units (U) lipase, respectively. The capsules contain identical pancrelipase formulated minitablets that are 2.0 mm in diameter. A stability study with the minitablets mixed in foods (i.e., applesauce, pudding, and yogurt) was conducted to support the use of various foods to administer the minitablets (see Section 5 Clinical Pharmacology).

Overview of Final Product Release and Packaging: Axcan Pharma US, Inc. is responsible for the final DP release and final 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) with (b) (4) In response to DTP's request, (b) (4) initiated an evaluation of the (b) (4) (b) (4) and (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 EMCF 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 [redacted] (b) (4) and [redacted] (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 [redacted] (b) (4) [redacted] (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 [redacted] (b) (4) were related to (see final wording of Items #1 to #19 in Deficiency Letter to [redacted] (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, [redacted] (b) (4) content, microbial limits), storage conditions, and expiration date; (3) process data for DS 1208 (a primary drug substance) and DS 1286 [redacted] (b) (4)); (4) rejected batches may not be reworked or reprocessed; (5) in-process lipase activity and microbial limits acceptance criteria; (6) [redacted] (b) (4) characterization study; (7) DS characterization for amylase; (8) DS 1286 release testing ; (9) specification for [redacted] (b) (4) content and impurities for release testing; (10) tightening of protease and amylase activity acceptance criteria; (11) [redacted] (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) [redacted] (b) (4) assay method used in the [redacted] (b) (4) step of manufacturing; (7) description of the [redacted] (b) (4) process for the [redacted] (b) (4) step of manufacturing; (8) information regarding the CMC for hypromellose phthalate used for the enteric coating of the minitablets; (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 ([redacted] (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 [redacted] (b) (4) were related to (see final wording of Items #15 to #21 in Deficiency Letter to [redacted] (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 [redacted] (b) (4) were related to (see final wording of Items #1 to #14 in Deficiency Letter to [redacted] (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 [redacted] (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 degration 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) (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 Other Issues (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 Current Review Cycle

In the current 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. (The reader is referred to the Drug Substance Non-Viral Issues Review dated April 28, 2010, the Drug Product Review dated April 30, 2010, the Drug Substance Viral Issues Review dated April 30, 2010, the Final Product Release and Packaging Review dated April 30, 2010, and the Microbiology Reviews dated March 29, 2010, and April 12, 2010 for complete information.)

3.3.1 DS Viral Issues (Current Cycle)

The DS Viral Issues reviewer noted that deficiencies exist, but do not preclude approval of the application since these can be addressed as postmarketing commitments (PMC's). (See DS Viral Issues Review by Howard Anderson dated April 28, 2010 for complete information.)

The PMC's recommended by the DS Viral Issues reviewer are provided below; this is followed by a summary of the DS Viral Issues reviewer's assessment of (b) (4) response to each deficiency item identified in the second review cycle.

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

DS viral items to be communicated to (b) (4) (taken from Dr. Anderson's review) as postmarketing commitments (PMC's) are provided below. (See also Section 13.6.)

PMC #1: Submit the final study reports of the cleaning agents effectiveness for viral inactivation for protocols # 09-VV-17-020 & 09-VV-12-121 to the FDA. (Final Report Submission date to be determined as per review.)

PMC #2: Submit the validation report for the PCV1 (Porcine Circovirus 1) infectivity release assay to the FDA. (Final Report Submission by December 2010 as per review.)

PMC #3: Establish lot release specifications for the PCV1 infectivity assay. (Final Report Submission by June 2011 as per review.)

PMC #4: Establish lot release specifications for the PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) infectivity assay. (Final Report Submission by October 2010 as per review.)

PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide better assurance that released drug substance will not contain EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reo Virus), Rota (Rota Virus), PTV (Porcine Teschovirus) viruses. Revise the assays, and submit assay validation data, together with acceptance criteria. (Final Report Submission date to be determined as per review.)

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

Reviewer's Assessment of (b) (4) Response (to Deficiency Items #15 to #21):

A summary of the DS Viral Issues reviewer's assessment of the adequacy of (b) (4) response to Items #15 to #21 in the letter to (b) (4) is presented below:

(15) Sanitizing procedures to prevent cross contamination between DS batches. The DS Viral Issues reviewer noted that (b) (4) proposed a study involving (b) (4) The DS Viral Issues reviewer noted that the (b) (4) material is representative of many of the product contact surfaces in the facility that pose the highest risk for viral contamination, and recommended that the results of this study be submitted as part of a PMC (see **PMC #1** above). The DS viral issues reviewer also noted that efficacy of selected cleaning agents will be tested by a contract laboratory, and that (b) (4) is evaluating the possibility of implementing a viral monitoring program of the cleaning methods.

(16) Development and validation of PCV1 infectivity assay. The DS Viral Issues reviewer noted that (b) (4) commits to develop and validate an infectivity assay for PCV1 by December 2010, and to submit a final report by June 2011; the DS Viral Issues reviewer recommended that these be communicated as PMC's in the approval letter (see **PMC's #2 and #3** above).

(17) Lot release specifications for PPV and PCV2. The DS Viral Issues reviewer noted that infectivity assays for PPV and PCV2 have been developed for DS 1208, and that (b) (4) commits to establish lot release specifications for PPV and PCV2 for DS 1286 by October 2010; the DS Viral Issues reviewer recommends that this be communicated as a PMC in the approval letter (see **PMC #4** above).

(18) Estimate of viruses per dose of DS, and proposal for appropriate control. The DS Viral Issues reviewer found (b) (4) response adequate as the information requested was provided. As part of their response, (b) (4) provided an estimated worst case exposure to patients for viruses (such as HEV, SVDV, EMCV, PTV, and rotavirus known to infect swine herds) and calculated (b) (4) for each of these viruses; the DS Viral Issues reviewer noted that these are worst case levels that go undetected because of the sensitivity of the viral monitoring assays, and suggested that improvement of the sensitivity of the assays (the next item) be addressed.

(19) Plans for improvement of sensitivity of qPCR assays for selected viruses. The DS Viral Issues reviewer noted that (b) (4) commits to revise the assay to improve the sensitivity of the qPCR assays used for DS release testing (i.e., to provide better assurance that released DS will not contain EMCV, HEV, SVDV, Reo, Rota, or PTV viruses) and to submit assay validation data and acceptance criteria. The DS Viral Issues reviewer recommends that this be communicated as a PMC in the approval letter (see **PMC #5** above).

(20) Risk assessment and control strategy for hokovirus. The DS Viral Issues reviewer noted that (b) (4) commits to assessing risk to product quality associated with porcine

hokovirus and providing a control strategy. The DS Viral Issues reviewer recommends that this be communicated as a PMC in the approval letter (see **PMC #6** above).

(21) Risk mitigation plan for new and emerging adventitious agents. (b) (4) response was deemed adequate. The DS Viral Issues reviewer noted that (b) (4) surveillance program involves the routine monitoring of public databases and publications that will alert (b) (4) to facilitate a plan for to mitigate the risk of contamination with new viral agents.

3.3.2 DS Non-Viral Issues (Current Cycle)

The DS Non-Viral Issues reviewer noted that a number of the deficiencies identified in the previous cycle were adequately addressed; however, a number of deficiencies still exist that preclude approval and should be communicated to (b) (4) (See Drug Substance Non-Viral Issues Review by Wei Guo dated April 30, 2010 for complete information.)

The deficiency items identified by the DS Non-Viral Issues reviewer are provided below; this is followed by a summary of the DS Non-Viral Issues reviewer's assessment of (b) (4) response to each deficiency item identified in the second review cycle.

Deficiency Items:

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

Item #1. You have developed a Reverse Phase HPLC assay to monitor product quality at release and during storage. For this assay, you propose acceptance criteria based on the mean peak area ± (b) (4) SD. Your proposed acceptance ranges are too wide and are not justified by your manufacturing history and process capability. Please revise your acceptance criteria for RP-HPLC to reflect manufacturing history and current estimate of process capability, and include the revised acceptance criteria in your release and stability protocols.

Item #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 propose expiry, you proposed a (b) (4) month retest date and a 24 month expiry, however, no data was provided in the submission. Please be aware that retest is generally not acceptable for protein products because protein product may undergo non linear degradation. Therefore, expiry should be established based upon real time stability data. Please provide 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 becomes available. Please be aware 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.

Item #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.

Item #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.

Reviewer's Assessment of (b) (4) Response to Deficiency Items #1 to #14**:**

A summary of the DS Non-Viral Issues reviewer's assessment of the adequacy of (b) (4) response to Items #1 to #14 in the letter to (b) (4) is presented below:

(1) RP-HPLC assay methods to monitor purity of DS 1286: A deficiency item should be communicated to (b) (4) The DS Non-Viral Issues Reviewer determined that one part of this item was not adequately addressed: (b) Regarding the concern that the acceptance criteria for some of the peaks are too wide allowing for 100-fold variability, (b) (4) stated that these acceptance criteria are based on the mean value and (b) (4) lots of DS 1208; the DS Non-Viral Issues Reviewer noted that the proposed acceptance ranges are too wide and are not justified by (b) (4) manufacturing history and process capability, and recommended that a deficiency item be sent to (b) (4) to revise their RP-HPLC acceptance criteria in their release and stability protocols (see **Item #1**). The DS Non-Viral Issues Reviewer determined that the remaining parts of this item were adequately addressed: (a) (b) (4) described the method used to calculate the peak ratio (i.e., integrate the area of each peak for the sample, normalize it, and divided by the area of the corresponding peak found in the reference standard); and (c) (b) (4) provided acceptance criteria for the additional peaks/peak groups that were excluded from analysis.

(2) RP-HPLC identity assay acceptance criteria: This item was adequately addressed as (b) (4) provided acceptance criteria based on peak area ratios rather than absorbance ratios.

(3) Validation of (b) (4) process of DS 1208: This item was adequately addressed as the validation report using three lots was provided to the DMF.

(4) Target lipase activity for glands used in manufacture of DS 1208: This item was adequately addressed. (b) (4) was requested to provide the target lipase activity for glands used in the DS 1208 manufacturing process. (b) (4) responded that glands of different grades (e.g., butcher glands, sow glands, and combinations) are used, and the target lipase activity is calculated using historical data for lipase units per pound from each grade of gland. The DS Non-Viral Issues Reviewer concluded that the response was adequate.

(5) RP-HPLC assay used in release and stability testing: This item was adequately addressed. (b) (4) provided the method validation report for the RP-HPLC assay used in release and stability testing. The DS Non-Viral Issues Reviewer noted that all validation criteria were met.

(6) Sample DS label: This item was adequately addressed as (b) (4) provided a sample drug substance label that included the following: manufacturer's name, address, drug substance name, storage conditions, expiration date, lot number, and weight.

(7) Forced degration studies to evaluate suitability of RP-HPLC assay for stability testing: This item was adequately addressed. (b) (4) provided results of forced degradation studies performed under four stress conditions (acid, alkaline, thermal, and oxidation); after exposure to the stress conditions, samples were examined using RP-HPLC and enzyme activity methods. The DS Non-Viral Issues Reviewer concluded that the response is adequate, and noted that both the RP-HPLC and enzymatic assay methods are complementary in the evaluation of the degradation profile of the DS.

(8) Clarification of term "finished product" in report: This item was adequately addressed. (b) (4) clarified that the term "finished product" referred to the final drug substance, and revised the study report accordingly.

(9) Acceptance criteria for release testing of DS 1208: The manufacturer was requested to provide acceptance criteria for DS 1208 with upper and lower limits for areas of peaks identified by RP-HPLC. (b) (4) responded that DS 1286, the (b) (4) form of DS 1208 lots, is used for NDA 22-222, and provided release specifications for DS 1286. The DS Non-Viral Issues reviewer commented that the RP-HPLC assay was performed only for limited time points, and requested additional stability data to support the proposed shelf life (see **Item #4** above).

(10) Olive oil testing program: The manufacturer was requested to monitor for critical olive oil attributes and to establish acceptance criteria for critical olive oil components. The response is adequate as the requested details (e.g., fatty acid composition by gas chromatography, and a characterization of olive oil using RP-HPLC) have now been included in the DMF.

(11) Enzyme assay method validation reports: (b) (4) provided enzyme assay method validation reports for its testing facility as requested; however, it also provided a second set of enzyme assay method validation reports for its contract testing facility, (b) (4) Even though both sets of reports were deemed acceptable by the DS Non-Viral Issues Reviewer, the response is not adequate because it is not clear whether (b) (4) (b) (4), or both sites will be used to perform the release assays; if both sites will be used, then data supporting the equivalency of the two sites will be required. Thus, the DS Non-Viral Issues Reviewer recommends a deficiency item be communicated to (b) (4) (see **Item #3** above).

(12) Expiry for DS 1208: This item was not adequately addressed. Regarding the request to identify an expiry or hold time for DS 1208 along with supporting data, the

manufacturer proposed a (b) (4) month retest date and a 24 month expiry without any supporting data. The DS Non-Viral Issues Reviewer recommends a deficiency item be communicated to (b) (4) (see **Item #2** above).

(13) Method to ensure accurate and consistent lipase activity for the working reference standard: This item was adequately addressed. Regarding the development of a working reference standard, (b) (4) responded that it uses the USP reference standard instead of an internal reference standard. The DS Non-Viral Issues reviewer noted that (b) (4) is one of the test laboratories to re-evaluate the USP reference standard, and thus the response is acceptable.

(14) Lipase activity results using (b) (4) - (b) (4) This item was adequately addressed. (b) (4) provided results showing that there are minimal differences in activation using the (b) (4) (b) (4) based on a study that included 40 batches of DS 1208 where half were manufactured using the (b) (4) (b) (4) and the other half were manufactured using the (b) (4))

3.3.3 DP Issues (Current Cycle)

The DP reviewer noted that a number of the deficiencies identified in the previous cycle were adequately addressed; however, some deficiencies still exist and should be communicated to Eurand. (See Drug Product Review by Wei Guo dated April 30, 2010 for complete information.)

The deficiency items identified by the DP reviewer are provided below; this is followed by a summary of the DP reviewer's assessment of Eurand's response to each deficiency item identified in the second review cycle.

Deficiency Items:

DP items to be communicated to Eurand (taken from Dr. Guo's review) as deficiency items are provided below. The DP Reviewer noted that both of these deficiencies can be easily addressed, including one item (Item #2 below) that could be addressed as a PMC once all deficiencies related to NDA 22-222 are resolved. (See also Section 13.1.)

Item #1. You have developed a Reverse Phase HPLC assay to monitor product quality at release and during storage. For this assay, you propose acceptance criteria based on the mean peak area ± (b) (4) SD. Your proposed acceptance ranges are too wide and are not justified by your manufacturing history and process capability. Please revise your acceptance criteria for RP-HPLC to reflect manufacturing history and process capability.

Item #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.

Regarding Item #2 above, the DP Reviewer notes that Eurand may not have all the information available on DS stability as the DS is manufactured by (b) (4) Thus, this item will likely have to be addressed as a PMC once all deficiencies related to NDA 22-222 are resolved.

Reviewer's Assessment of Eurand's Response to Deficiency Items #1 to #6**:**

A summary of the DP reviewer's assessment of the adequacy of Eurand's response to Items #1 to #6 in the letter to Eurand is presented below:

(1) Release testing data: Eurand was requested to provide data from release tests performed on the encapsulated product. Eurand responded that enzymatic activities of the encapsulated product are calculated from the activity value for the coated minitablets and the average capsule filling weight. The DP reviewer commented that this is not a valid method to find enzymatic activity of the encapsulated product, but determined that this is not a deficiency item because the final DP release testing is done by the NDA holder.

(2) Microbial limit testing results per lot: Eurand was requested to provide results of microbial limit testing performed on every lot manufactured, and to include the results in their Certificate of Analyses. Eurand's response included an assertion that each batch of packed drug product is tested for microbiology purity by the NDA holder before its final release. The DP reviewer concluded that Eurand's response is acceptable after he consulted with the Microbiology Reviewer (Stephen Langille); the DP reviewer noted that all lots on the final release of the drug product would be tested and that microorganisms are not likely to grow under the dry conditions of the pancrelipase capsules.

(3) Release test sampling methods: Eurand was requested to demonstrate homogeneity of bulk drug product capsule samples during the capsule filling, by analyzing sample capsules taken at the beginning, middle and the end of the filling process. Eurand provided data on four lots of encapsulated drug product from one batch of coated minitablets. The DP Reviewer noted that the data showed high consistency in activities and capsule weight, and concluded that the response was acceptable.

(4) Release and stability acceptance criteria for the RP-HPLC assay: Regarding the concern that the release and stability acceptance criteria for the RP-HPLC assay are not adequate, Eurand responded that these acceptance criteria are based on the mean value and (b) (4) DS lots; the DP Reviewer noted that the proposed acceptance ranges are too wide and did not demonstrate adequate control of product quality. The DP Reviewer recommended that a deficiency item be sent to Eurand to revise their RP-HPLC acceptance criteria in their release and stability protocols (see **Item #1** above).

(5) Acceptance criteria for moisture content: Eurand was requested to revise acceptance criteria for moisture content to reflect process capability and historical results. Eurand responded with a revised acceptance limit of no more than (b) (4)%. The DP Reviewer found the response acceptable.

(6) Data collected using the updated stability program and acceptance criteria: Eurand was requested to provide data collected using the updated stability program and acceptance criteria. Eurand provided stability data using the RP-HPLC assay. The DP reviewer commented that the RP-HPLC assay was performed only for limited time points, and requested additional stability data to support the proposed shelf life (see **Item #2** above).

3.3.4 Final Product Release and Packaging Issues (Current Cycle)

The Final Product Release and Packaging reviewer noted that many of the deficiencies identified in the previous cycle were adequately addressed; however, a deficiency still exists that should be communicated to the Applicant (Axcan Pharma US, Inc.). (See Final Product Release and Packaging Review by Wei Guo dated April 30, 2010 for complete information.)

The deficiency item identified by the Final Product Release and Packaging reviewer is provided below; this is followed by a summary of the Final Product Release and Packaging reviewer's assessment of Axcan Pharma's response to each deficiency item identified in the second review cycle.

Deficiency Items**:**

A Final Product Release and Packaging deficiency item to be communicated to Axcan Pharma (taken from Dr. Guo's review) is provided below. (See also Section 13.1.)

Item #1. 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.

Reviewer's Assessment of Axcan Pharma's Response to Deficiency Items #2 to #5**:**

A summary of the Final Product Release and Packaging reviewer's assessment of the adequacy of Axcan Pharma's response to Items #2 to #5 in the CR letter to Axcan Pharma is presented below:

(2) Clarification regarding stability testing (should be performed on packaged DP not prior to packaging): This item has been adequately addressed. The Applicant clarified that all stability studies have been performed on packaged drug product using the final container/closure system.

(3) Data collected using the updated stability program and acceptance criteria: This item has been adequately addressed. The Applicant has provided updated stability summary data and acceptance criteria for three MT 12 lots.

(4) Stability once final container opened (forced degradation studies): This item has been adequately addressed. The Applicant conducted temperature excursion and thermo

cycling studies, cold storage conditions at 5°C studies, an in-use stability study, and a photostability study. Results of each of the studies were deemed acceptable by the Final Product Release and Packaging reviewer.

(5) Stability data for 12 count bottle to support 16-month expiry (or revise label to state 12 month expiry): This item has been adequately addressed. The firm agrees to revise the 12 count bottle label to a 12 month expiry until further stability data is provided to support a longer expiry date.

An additional item was noted by the final product release and packaging issues reviewer during the course of this review:

- Additional Item: The Final Product Release and Packaging reviewer noted a discrepancy in the description of the capsules printing between the Applicant's NDA submission and the description provided in the package insert (e.g., for the lowest dosage strength formulation, the PI states that "AXCA" is printed on the capsule body whereas the NDA states that "MT 12" is printed on the capsule body; and the PI states that "13800UL" is printed on the capsule cap whereas the NDA states that "ULTRASE" is printed on the capsule cap). (See **Item #1** above.)

3.3.5 Microbiology Issues (Current Cycle)

Two reviews were written by the Microbiology reviewer, one filed in the NDA and one filed in the DMF for (b) (4)

The Microbiology Reviewer provided the following background of the microbiology issues (see review by Stephen Langille dated March 29, 2010; NDA 22-222): The results of recent testing done by the FDA's Southwest Regional Lab show that one of seven drug substance samples obtained from (b) (4) was positive for *Bacillus cereus* enterotoxin. The microbiology reviewer notes that Bacillus cereus diarrheal enterotoxin is heat labile at temperatures greater than 133°F (56°C) (Schneider et al, Preventing Foodborne Illness: Bacillus cereus and Bacillus anthracis. IFAS Extension, 2004).

Memo filed in the NDA:

In the memo filed in the NDA, the Microbiology reviewer recommended that each lot of drug substance manufactured at (b) (4) have a release specification for the absence of *B. cereus* enterotoxin for the following reasons: (1) One of the seven samples of drug substance obtained from (b) (4) has tested positive for the presence of B. cereus enterotoxin. It's not clear if the presence of the toxin in this sample is an aberration or a common event. (2) Subject matter experts at CDER and CFSAN agree that the presence of *B. cereus* enterotoxin in Pancrelipase drug product could result in significant gastrointestinal adverse events or systemic illness, particularly in immunocompromised patients. (3) (b) (4) be responsible for *B. cereus* growth and toxin production during drug substance processing. Further, (b) (4) employed at (b) (4) may allow the heat labile toxin to survive processing. (4) The drug product manufacturing process does not appear to include (b) (4)

(b) (4) (5) (b) (4) has been reluctant to address the product quality deficiencies identified in the Drug Master File.

The Microbiology reviewer also recommends that an amendment be submitted to the DMF indicating the methods used for sampling and testing the bulk drug substance for enterotoxin. The submission should include the reliability (repeatability) and sensitivity of the method in (b) (4) hands. The specificity of the method can be provided from available literature. The results of this testing should be included in the Certificate of Analysis provided with each lot of bulk drug substance. A review of the batch records from the offending lot and lots that do not show the presence of enterotoxin may yield the cause of increased B. cereus toxin levels. This specification could be relaxed or eliminated if the cause of the enterotoxin contamination can be determined and corrective actions taken.

The microbiology reviewer stated that the recommendations in the memo filed in the NDA would be communicated to (b) (4) through the Office of Compliance.

Memo filed in the DMF:

The DMF deficiency items identified by the Microbiology reviewer are provided below (see review by Stephen Langille dated April 12, 2010; DMF (b) (4) this is followed by a summary of the Microbiology reviewer's assessment of (b) (4) response to each deficiency item identified in the second review cycle.

Deficiency Items (from the DMF Review):

Microbiology items to be communicated to (b) (4) (taken from Dr.Langille's review) as deficiency items are provided below. (See also Section 13.1.)

Item #1. Provide a justification for all in-process holding times associated with the manufacture of Pancreatin. The processing times and holding conditions prior to the (b) (4) (b) (4) step" are of particular importance since most of the microbial proliferation occurs during that stage of the manufacturing process.

Item #2. Step f) (1) of the 1208 process description states that " (b) (4) (b) (4) (b) (4) (b) (4)

Item #3. Provide the following information regarding in-process microbial alert and action levels

a. Total aerobic microbial count (TAMC) alert and action levels for processes 1206 and 1208 at the process points indicated in tables 8 (p. 771-772) and 10 (pp. 824-827) of the January 4 2010 update to DMF (b) (4)
b. TAMC alert and action levels for samples of the (b) (4) collected immediately prior to (b) (4)
c. A summary of the steps taken when alert and action levels are exceeded

Item #4. 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 diarrheal enterotoxin prior to release
b. A description of the Bacillus cereus diarrheal enterotoxin test method, the validation procedure, and a summary of the supporting validation data.

Reviewer's Assessment of (b) (4) Response to Deficiency Items #22 and #23:

A summary of the Microbiology reviewer's assessment of the adequacy of (b) (4) response to Items #22 and #23 in the Letter to (b) (4) is presented below.

(22) Washing, processing, and microbiological acceptance criteria for pancreas glands: This item has been adequately addressed. (a) (b) (4) provided an explanation of the procedures in place prior to (b) (4) The glands are (b) (4) prior to (b) (4) (b) (4) explains that the "recommended" method of gland collection is to (b) (4) All pancreas glands are sourced from the (b) (4) and glands may only be collected from (b) (4) acceptable hogs and inspected and/or approved slaughterhouses/packing plants. (b) (b) (4) provided an explanation of its microbiological acceptance criteria; (b) (4) explained that because a single lot consists of (b) (4) glands, sampling and testing of individual glands is impractical, so instead (b) (4) samples and tests for bioburden early in the drug substance manufacturing process at the (b) (4) and prior to the (b) (4) (b) (4) step. (b) (4) provided microbial limits for the drug substance (based on total aerobic microbial count [TAMC], bile tolerant gram negative bacteria, Aeromonas species, Enterobacter sakazakii, E. coli, Salmonella, and Enterococci). The microbiology reviewer noted that the microbial limits provided by (b) (4) are release specifications for the finished DS, and that microbial counts during manufacture of the bulk DS exceeded these limits; however, the microbiology reviewer stated that the fact that the TAMC for the (b) (4) of manufacturing processes 1206 and 1208 were not extraordinarily high (b) (4) CFU/g) suggests that the pancreas glands are not grossly contaminated upon arrival at (b) (4) and thus deemed the response satisfactory.

(23) Information about manufacturing process (including storage time, temperature, and data showing effect of storage on microbial growth): This item was not adequately addressed. The microbiology reviewer noted that (b) (4) failed to demonstrate microbiological control of the drug substance during the (b) (4) of the (b) (4) (b) (4)). These storage temperatures are similar to those used during the 1206 manufacturing process ((b) (4) °C) which demonstrated (b) (4) increases in total aerobic microbial over a period of < (b) (4). Holding periods of (b) (4) even at (b) (4), could result in substantial microbial growth in the (b) (4) The microbiology reviewer stated that (b) (4) should provide a list of corrective actions to be taken to ensure control of microbial growth during storage of the (b) (4) (see **Item #1** above).

Additional issues were noted by the microbiology reviewer during the course of this review:

- Because there is limited microbiological control of the drug substance manufacturing process and the source of Bacillus cereus enterotoxin can not be identified at this time, each lot of Pancreatin drug substance should be tested for Bacillus cereus enterotoxin prior to release (see **Item #4** above).
- Step f) (1) of the 1208 process description states that "[redacted] (b) (4) [redacted]". However, [redacted] (b) (4) did not provide the maximum storage time for the 1208 [redacted] (b) (4) prior to [redacted] (b) (4) or the results of studies to show that there is no significant microbial proliferation during the storage period. Efforts should be made to limit the storage time of the [redacted] (b) (4) prior to [redacted] (b) (4) (See **Item #2** above.)
- In-process microbial alert and action levels should be implemented to improve the microbiological purity of the finished drug product (see **Item #3** above).

3.3.6 Other Issues (Current Cycle)

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

[redacted] (b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation for [redacted] (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 [redacted] (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 [redacted] (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 Final Recommendation

A Complete Response Action is the final recommendation by CMC.

Deficiency items to be communicated to the Applicant (NDA 22-222), to the drug substance DMF holder (# (b) (4) and to the drug product DMF holder (# 15681) are provided in Sections 13.1.1, 13.1.2, and 13.1.3, respectively.

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[6], given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Ultresa clinical development 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:

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

- Indications and Usage section of Highlights: "Pancreatic enzyme preparation digestant" is recommended as the established pharmacologic class.
- 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."

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

4.2 Second Review Cycle

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

4.3 Current Review Cycle

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

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

4.4 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline provided the labeling revisions described above are made.

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 minitablets in Ultresa Capsules is designed to dissolve at 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 minitablets were stable in chocolate pudding (approximate 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., minitablets 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 100^0C 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 37^0C.
- 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 minitablet 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 minitablets can only be mixed with acidic food (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.

Since Ultresa was not recommended for Approval during the second review cycle, labeling changes were not negotiated with the Applicant.

5.3 Current Review Cycle

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

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

5.4 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology discipline provided the labeling revisions described above are made.

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; CF-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 (Pivotal Study; Study CF-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

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
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	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-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 ≤40%),
- moderately-affected (>40 and ≤80%), and
- mildly-affected (>80%).

The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of ≤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 ≥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 is not 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 Review Cycle

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

7.3 Current Review Cycle

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

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

7.4 Final Recommendation

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

8. Safety

The reader is referred to the CDTL Review by Anne Pariser dated July 1, 2008, the Clinical Review by Joanna Ku dated July 1, 2008, and the Clinical Reviews of Safety Updates by Ali Niak, dated September 9, 2009, March 9, 2010, and April 30, 2010 for complete information.

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

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

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

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

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

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

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.

- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g., pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.

- Irritation to Oral Mucosa: Disruption of the protective enteric coating, and early release of the enzymes may lead to the irritation of the oral mucosa as well as loss of enzyme activity.

The theoretical risk of viral transmission is summarized below:

- Theoretical Risk of Viral Transmission: There is a concern that because PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[10,11] (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 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 Review Cycle

The reader is referred to the Clinical Review of Safety Update by Ali Niak, dated September 9, 2009 for complete information.

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

Dr. Niak 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; a literature search was also provided.

Postmarketing Experience: Dr. Niak notes that based on US unit sales of Ultrase® MT Capsules during the reporting period (December 1, 2007 through September 30, 2008), patient exposure was estimated to be approximately 7,058 patient-treatment-years. 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 30th percentile); weight was selected based on age and weight data in the Cystic Fibrosis Foundation (CFF) Registry. It should be noted that US sales of Ultrase® MT Capsules constitute the greatest percentage globally (more than (b)(4)%) although Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile and Canada).

For Ultrase® MT, a total of 17 case reports of adverse events were received. Two of the case reports were serious (severe abdominal pain in a 71-year-old male, and diarrhea/abdominal discomfort in an18-month old); for each of the patients, no information was provided regarding medical history and indication. Diarrhea and abdominal pain are known to be associated with EPI and have also been described in clinical trials of the two available approved PEPs (Zenpep and Creon) at the time of the second review cycle. These reports may represent under-treatment; however, given the limitations of the postmarketing safety information provided (e.g., lack of information about dose, treatment duration, and co-morbid conditions) as well as general limitations of postmarketing information (e.g., difficulty estimating reporting rate and denominator), etiology cannot be determined. Nevertheless, bacterial contamination of the drug substance (see Section 3.2.6) cannot be ruled out as a possible etiology for these cases. Fifteen of the case reports were non-serious (predominantly gastrointestinal signs and symptoms and/or lack of efficacy) spontaneous reports; no information was provided regarding medical history and indication. The most frequently reported adverse events were diarrhea (5), followed by lack of efficacy (4), abdominal pain (3), erythema (3), and generalized pruritus (2). The remaining cited adverse events were single occurrences. The pattern of common adverse events appeared to be similar to that described in the labeling for the two available approved PEPs (Zenpep and for Creon) at the time of the second review cycle; the clinical reviewer noted that there appeared to be more cases of diarrhea in the postmarketing reports for Ultrase than that described in the labeling for Zenpep and for Creon. However, given the limitations of the postmarketing information provided as well as the small size of the clinical trials of Creon and of Zenpep, it is not possible to draw a clear conclusion regarding relative rates of the adverse events. It should also be noted that bacterial contamination of the drug substance (see Section 3.2.6) cannot be ruled out as a possible etiology for the adverse events reported.

Clinical Study Update: A safety update to September 30, 2008, was provided for Study UMT20CF07-01, a completed study of CF patients aged 7 to 11 years old using Ultrase® MT20, the HP55 coated formulation that is the same as the CMP. Nine patients were enrolled; two patients discontinued due to AEs (one patient was an 11 year old male with

sinusitis; the other patient was a 7 year old male with streptococcus pharyngitis). The investigator and the clinical reviewer deemed these AEs unrelated to Ultrase® MT.

Literature Update: The Applicant conducted a search of the medical literature for the period from December 2, 2007, to October 31, 2008. The Applicant stated that the literature search did not provide any new relevant safety information pertaining to Ultrase® MT or other formulations of pancreatic enzyme preparations.

8.3 Current Review Cycle

The reader is referred to the Clinical Reviews of Safety Updates by Ali Niak, dated March 9, 2010 and April 30, 2010 for complete information.

Dr. Niak 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; a literature search was also provided.

Three safety updates were reviewed. The first Safety Update covered the period from November 1, 2008, to May 31, 2009, for post-marketing information, and from October 1, 2008 to May 31, 2009, for clinical study information. The second Safety Update covered the period from June 1, 2009, through November 3, 2009 for post-marketing information, and from June 1, 2009, to November 3, 2009, for clinical study information. The third Safety Update covered the period from November 1, 2009, to January 31, 2010, for post-marketing information, and from November 1, 2009, to January 31, 2010, for clinical study information.

Postmarketing Experience: Dr. Niak notes that based on US unit sales of Ultrase® MT Capsules patient exposure was estimated to be approximately 6,872, 4,501, and 3,362 patient-treatment-years for the reporting periods of the first, second, and third Safety Updates, respectively. 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 30th percentile); weight was selected based on age and weight data in the Cystic Fibrosis Foundation (CFF) Registry. It should be noted that US sales of Ultrase® MT Capsules constitute the greatest percentage globally (more than (b)(4)%) although Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile and Canada).

For Ultrase® MT, a total of 11, 21, and 10 case reports of adverse events were received in the reporting periods of the first, second, and third Safety Updates, respectively. One serious case involving Ultrase® MT (ischemic colitis in a 71-year-old female manifested as thickening and ulcers in the descending colon) was reported in the second Safety Update; no information was provided regarding medical history, indication, and concomitant medication. The clinical reviewer notes that the case was medically confirmed. No serious cases were reported in either of the other two Safety Updates. Given the limitations of the postmarketing safety information provided (e.g., lack of information about dose, treatment

duration, and co-morbid conditions) as well as general limitations of postmarketing information (e.g., difficulty estimating reporting rate and denominator), etiology cannot be determined with certainty. Nevertheless, bacterial contamination of the drug substance (see Sections 3.3.5 and 3.3.6) cannot be ruled out as a possible etiology for the serious case reported. Eleven, ten, and twenty of the case reports (from the first, second, and third Safety Updates, respectively) were non-serious (predominantly gastrointestinal signs and symptoms and/or lack of efficacy) spontaneous reports; no information was provided regarding medical history and indication. In the first Safety Update, the most frequently reported adverse event was drug ineffective (4). In the second Safety Update, the most frequently reported adverse events were diarrhea (5), followed by frequent bowel movement (4), abdominal distension (2), abnormal feces (2), malabsorption (2), steatorrhea (2), and drug ineffective (2). In the third Safety Update, the most frequently reported adverse events were diarrhea (3), followed by abnormal feces (2). In each of the Safety Updates, the remaining cited adverse events were single occurrences. The pattern of common adverse events appeared to be similar to that described in the labeling for the three currently available approved PEPs (Zenpep, Creon, and Pancreaze). Given the limitations of the postmarketing information provided as well as the small size of the clinical trials of Creon, Zenpep, and Pancreaze, it is not possible to draw a clear conclusion regarding relative rates of the adverse events. It should also be noted that bacterial contamination of the drug substance (see Sections 3.3.5 and 3.3.6) cannot be ruled out as a possible etiology for the adverse events reported.

Clinical Study Update: There was no new information for completed studies in any of the three Safety Updates. Each of the Safety Updates had information for the ongoing study UMT12CF08-01 in 2 to 6 year old CF patients. Fifty-four patients were enrolled, 5 failed screening procedures, and 4 were withdrawn before completing the study; reasons for withdrawal from the study are not provided. The Safety Update states that the clinical study report is under preparation.

Literature Update: The first and third Safety Updates stated that the literature searches did not provide any new relevant safety information pertaining to Ultrase® MT or other formulations of pancreatic enzyme preparations. In the second safety update, seven articles were cited and discussed. The clinical review of the Safety Update dated March 9, 2010 provides a discussion of these articles.

8.4 Final Recommendation

Should Ultresa receive an Approval action during a subsequent review cycle, a Risk Evaluation and Mitigation Strategy (REMS) is recommended to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients (see Deficiency Item #6 in Section 13.1 Recommended Regulatory Action, and see Section 13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements).

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

During the course of the review, 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. The Division's new proposal for labeling for pediatric patients largely based on that consult review will be presented to PeRC in a subsequent review cycle.

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.

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 two 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 ber 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 ber 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 8: 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.

Subsequent Review Cycle:

In a subsequent review cycle, the application will be presented again to the Pediatric Research Committee (PeRC). In addition, the proposed labeling changes will be planned for negotiation with the Applicant should Ultresa receive an Approval action during a subsequent review cycle.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. 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 4. 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	Protocol violations: (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. Overall assessment: The data from this site can be used in support of the NDA.
Site 03 Steven Strausbaugh, MD Cleveland, OH	Six	Minor protocol violations: Two patients enrolled before results of fecal elastase results available; results later found to be within the protocol requirement. Overall assessment: The data from this site can be used in support of the NDA.

Information in the table above is taken from the CTDL 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 will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010.

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

11.4 Facilities Inspection

During a recent inspection of the (b) (4) ((b) (4) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility; based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation for (b) (4) Satisfactory resolution of these deficiencies is required before this application may be approved.

12. Labeling

12.1 Proprietary name

<u>Initial Review Cycle:</u>

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 previous review cycle, no trade name had been agreed upon with the Applicant.

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.

Current Review Cycle:

The proprietary name "Ultresa" was deemed acceptable before the start of the current 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).]

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

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

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

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The CMC Reviewer (of Final Product Release and Packaging) recommends this NDA for CR largely because of the deficiencies identified in the Drug Substance reviews. Microbiology drug substance deficiencies (identified by the Microbiology reviewer) and non-viral drug substance deficiencies (identified by the Drug Substance Non-Viral Issues Reviewer) will be communicated in a separate letter to the drug substance DMF Holder, (b) (4) (DMF (b) (4) In addition, drug product deficiencies (identified by the Drug Product Reviewer) will be communicated in a separate letter to the drug product DMF Holder, Eurand (DMF 15681),

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

13.1.1 CR Letter to Axcan Pharma US, Inc. (NDA 22-222)

CMC Deficiencies**:**

1. The [redacted] (b) (4) ([redacted] (b) (4) DMF # [redacted] (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 [redacted] (b) (4) and EURAND listing the deficiencies. [redacted] (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when [redacted] (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.

Clinical Deficiencies**:**

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 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.

4. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit 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.

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

Microbiology DS Deficiencies:

[The microbiology DS deficiencies below were sent to (b) (4) (DMF (b) (4) in a letter dated May 3, 2010.]

1. Provide a justification for all in-process holding times associated with the manufacture of Pancreatin. The processing times and holding conditions prior to the "(b) (4) (b) (4) step" are of particular importance since most of the microbial proliferation occurs during that stage of the manufacturing process.

2. Step f) (1) of the 1208 process description states that "(b) (4) ". Provide the maximum storage time for the 1208 (b) (4) prior to (b) (4)

3. Provide the following information regarding in-process microbial alert and action levels
   a. Total aerobic microbial count (TAMC) alert and action levels for processes 1206 and 1208 at the process points indicated in tables 8 (p. 771-772) and 10 (pp. 824-827) of the January 4 2010 update to DMF (b) (4)
   b. TAMC alert and action levels for samples of the (b) (4) collected immediately prior to (b) (4)
   c. A summary of the steps taken when alert and action levels are exceeded.

4. 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 diarrheal enterotoxin prior to release
   b. A description of the Bacillus cereus diarrheal enterotoxin test method, the validation procedure, and a summary of the supporting validation data.

Non-Viral DS Deficiencies:

[The non-viral DS deficiencies below were sent to (b) (4) (DMF (b) (4) in a letter dated May 4, 2010.]

1. You have developed a Reverse Phase HPLC assay to monitor product quality at release and during storage. For this assay, you propose acceptance criteria based on the mean peak area ± (b) (4) SD. Your proposed acceptance ranges are too wide and are not justified by your manufacturing history and process capability. Please revise your acceptance criteria for RP-HPLC to reflect manufacturing history and current estimate of process capability, and include the revised acceptance criteria 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 propose expiry, you proposed a (b) (4) month retest date and a 24 month expiry, however, no data was provided in the submission. Please be aware that retest is generally not acceptable for protein products and because protein product may undergo non linear degradation. Therefore, expiry should be established based upon real time real temperature storage conditions stability data. Please provide data to supporting 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 becomes available. Please be aware 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.

13.1.3 Deficiency Letter to Eurand (DMF 15681)

DP Deficiencies:

[The DP deficiencies below were sent to Eurand (DMF 15681) in a letter dated May 4, 2010.]

1. You have developed a Reverse Phase HPLC assay to monitor product quality at release and during storage. For this assay, you propose acceptance criteria based on the mean peak area ± (b) (4) SD. Your proposed acceptance ranges are too wide and are not justified by your manufacturing history and process capability. Please revise your acceptance criteria for RP-HPLC to reflect manufacturing history and process capability.

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.

13.2 Risk Benefit Assessment

The benefit characteristics appear similar to those of already marketed PEPs for treatment of EPI. The outstanding risk issues with this application are the significant deficiencies identified from the Microbiology discipline (failure by the drug substance manufacturer to adequately ensure the microbial quality of the drug substance) and the CMC discipline (inadequate release and stability testing for the drug substance and the drug product).

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

See Deficiency Item #3 (in CR Letter to Axcan Pharma US, Inc.) in Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since Ultresa is not recommended for Approval during this review cycle, recommendations for postmarketing pediatric requirements such as development of an age appropriate formulation will be made should Ultresa receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

> As described in our action letter dated September 9, 2009, in accordance with section 505(o)(3) of the FDCA, we have determined that, if this application is approved, you will be required to conduct the following postmarketing studies of Ultresa (pancrelipase) to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients taking Ultresa (pancrelipase) Delayed-Release Capsules:
>
> 1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultresa (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.
>
> 2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Ultresa (pancrelipase) Delayed-Release Capsules.
>
> The specific details of these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

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

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995[12]) 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[13] 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[14] states:

> "A 1995 consensus conference on the use of pancreatic-enzyme supplements sponsored by the U.S. Cystic Fibrosis Foundation recommended that the daily dose of pancreatic enzymes for most patients remain below 2500 units of lipase per kilogram

[12] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.

[13] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.

[14] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations."

APPENDIX 2: 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) (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) 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 [redacted] (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 [redacted] (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 minitablets.

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 minitablets.

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) ime 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) (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 [redacted] (b) (4)

   a. Are the glands washed or processed in any way prior to [redacted] (b) (4),

   b. Are microbiological acceptance criteria in place for the pancreas glands?

23) Section 3.2.S.2.1.2.2 of DMF [redacted] (b) (4) states that the maximum length of the [redacted] (b) (4) pancrelipase manufacturing process is [redacted] (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 [redacted] (b) (4) stored in [redacted] (b) (4) drums

   c. Data showing that the [redacted] (b) (4) stored in the [redacted] (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 [redacted] (b) (4) DMF # [redacted] (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 [redacted] (b) (4) and EURAND listing the deficiencies. [redacted] (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when [redacted] (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: Dosing Calculations - Children 1 to 10 Years Old

The table below is modified from a handout provided by Elizabeth Durmowicz during a labeling meeting for Ultresa:

Dosing Calculations for Girls, 1 To 10 Years Old[1]

Age (yrs)	**Weight** (kg)	**Weight Based Dosing[2]**	**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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

ANIL K RAJPAL
05/05/2010

Medical Officer's Review of Safety Update Report

NDA #:	22-222
Applicant:	Axcan Pharma US, Inc.
Product:	ULTRASE® MT / ULTRASE
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted/Received:	March 9, 2010
PDUFA Date:	May 5, 2010
Date of Review:	April 30, 2010
Clinical Reviewer:	Ali Niak, M.D., Medical Officer, DGP
Through:	Anil Rajpal, M.D., Acting Team Leader, DGP

BACKGROUND

ULTRASE® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been available on the United States (US) market since November 1991. Axcan Pharma Inc. has been marketing ULTRASE® MT Capsules since August 1999 in the US. In addition, ULTRASE® is currently marketed in Canada, Argentina, Brazil and Chile.

SAFETY UPDATES

A Safety Update was submitted by the Sponsor on March 9, 2010. The Safety Update covered the period from November 1, 2009, to January 31, 2010, for post-marketing information, and from November 1, 2009, to January 31, 2010, for clinical study information. Pertinent findings from the Safety Update are presented below.

Completed Clinical Study Update

Study UMT20CF07-01 is a multicenter, open-label, Phase 3 trial designed to establish the efficacy and safety of ULTRASE® MT20 (enteric coated with HP-55, the formulation currently on the market) in cystic fibrosis children aged 7-11 years old, with presence of pancreatic insufficiency. A total of 8 patients were initially planned to be enrolled with the expectation that approximately 5 patients would complete the study. The initial protocol was submitted to IND 41,387 on May 7, 2007 (Serial 070). Subsequently, the protocol was amended to include clarifications and minor editorial changes (Protocol Amendment – Serial 075, dated June 22, 2007). No further changes were made to the amended protocol dated June 22, 2007.

This study was initiated on July 28, 2007, in the US. At study completion in March 2008, 9 patients were screened; 7 patients were included in the Intent-To-Treat (ITT) population, and 3 were included in the Per Protocol (PP) Population. The PP Population included patients for whom both inpatient periods (washout and treatment phases) were completed, all bowel movements were collected and no major protocol violations occurred. The database was locked on May 30, 2008, and the data was analyzed by (b) (4) The results obtained from the statistical analysis became available on June 20, 2008. The clinical study report for this study was completed and approved on March 2, 2009.

The demographics and status of patients at the end of study are provided in Table 1 below.

Table 1. Demographics and status of patients enrolled in study UMT20CF07-01.

Subject No.	Gender	Ethnicity	Age (years)	BMI	PATIENT STATUS
0201	Male	Caucasian	11.5	17.2	Study completed
0202	Male	Caucasian	11.5	18.5	Study completed
0301	Male	Caucasian	11.5	15.9	Study completed
0302	Male	Caucasian	10.9	14.4	Study completed
0303	Male	Caucasian	11.4	15.8	Discontinued
0401	Male	Caucasian	7.6	15.1	Discontinued
0402	Male	Caucasian	10.0	17.6	Study completed
0403	Male	African	11.1	18.6	Study completed
0404	Male	Caucasian	7.6	14.6	Study completed

(Table above is taken from Page 5 of the NDA 22-222 Safety Update dated December 9, 2008.)

No patient died or experienced serious adverse events during this clinical study. Two patients (#0303 and #0401) did not complete the study because of adverse events. Patient #0303 developed sinusitis and was treated with antibiotics and patient #0401 developed a Streptococcal throat infection and was treated accordingly with antibiotics as well. The above two events do not appear to have been related to ULTRASE®.

Ongoing Clinical Study Update

Study UMT20CF08-01 is a multicenter, open-label, Phase IIIb trial designed to establish the efficacy and safety of ULTRASE® MT12 (enteric coated with HP-55, the formulation currently on the market) in the control to steatorrhea in cystic fibrosis children with pancreatic insufficiency. A total of 54 patients between 2 to 6 years of age enrolled in the study, of which, 5 of them failed the screening procedures and 4 were withdrawn before completing the study. In total, 45 patients completed the subject. The initial protocol was submitted to IND 41,387 on November 11, 2008 (Serial 086). Subsequently, the protocol was amended to include clarifications on the high fat diet, to better define the "optimized dose" of lipase to be used, to provide an objective criteria that will be used to determine this 'optimized dose' in order to not exceed the current Cystic Fibrosis Foundation guideline for maximum dosing to minimize the risk of fibrosing colonopathy (2500 Units of lipase/kg of body weight/meal or snack), and to include minor editorial changes (Protocol Amendment – Serial 087 dated February 28, 2009).

The enrolment of patients started on April 29, 2009, and was completed on September 25, 2009. The last subject completed the study on November 4, 2009. The database was closed on January 12, 2010. The clinical study report is under preparation.

ADVERSE EVENTS

Completed Clinical Study Update

Between November 1, 2009, and January 31, 2010, Axcan Pharma Inc. and its subsidiaries received 16 initial and one follow-up adverse event reports; additionally, a total of 27 adverse events were also reported. From these reports, 10 involved ULTRASE®, 5 involved VIOKASE®, one involved PANZYTRAT® and one involved pancreatic enzymes unspecified. No serious adverse event was received during the reporting period.

The table below presents the adverse events of all three products recorded in the database classified by body system (MedDRA standard organ system classification scheme (SOC)) during the period from November 1, 2009, to January 31, 2010.

Table 2. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from November 1, 2009, to January 31, 2010.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Pancreatic enzymes unspecified	Total
Gastrointestinal disorders					
Abdominal discomfort	0	1	0	0	1
Abdominal distension	1	1	0	0	2
Abdominal pain	0	1	0	0	1
Abdominal pain upper	2	0	0	0	2
Abnormal faeces	1	0	0	0	1
Change in bowel habit	1	0	0	0	1
Constipation	1	0	0	1	2
Diarrhoea	3	1	1	0	5
Dyspepsia	1	0	0	0	1
Flatulence	1	0	0	0	1
Nausea	0	2	0	0	2
General disorders and administration site conditions					
Condition aggravated	1	1	0	0	2
Drug effect decreased	0	1	0	0	1
Medication residue	0	1	0	0	1
Withdrawal syndrome	1	0	0	0	1
Injury, poisoning and procedural complications					
Expired drug administered	0	1	0	0	1
Musculoskeletal and connective tissue disorders					
Arthralgia	1	0	0	0	1
Skin and subcutaneous tissue disorders					
Rash	1	0	0	0	1
Total	**15**	**10**	**1**	**1**	**27**

Coded with MedDRA dictionary

(Table above is taken from Page 6 of the Safety Update for NDA 22-222 dated March 9, 2010.)

For ULTRASE, the most frequently reported adverse event was diarrhea (3). The next most frequently reported adverse event was upper abdominal pain (2). The remaining adverse events were single occurrences. Please refer to the above table.

The above adverse events may have been related to ULTRASE, to a class effect, or to the underlying condition of exocrine pancreatic insufficiency. Contamination of the drug substance with *Bacillus cereus* and/or enterotoxin cannot be ruled out as a possible etiology for the adverse events reported; contamination of the drug substance was raised as a concern on inspection of the drug substance manufacturing facility ((b) (4) DMF # (b) (4) (See also Consult Review from Division of Anti-infective and Ophthalmology Products [DAIOP] by Benjamin Lorenz dated June 5, 2009 and Health Hazard Evaluation by Anil Rajpal dated February 23, 2010.) The limited adverse event data

presented above are consistent with the known adverse event profile of pancreatic enzyme products (PEPs).

CUMULATIVE SALES AND EXPOSURE

An estimate of the patient exposure to ULTRASE® MT Capsules was calculated for the period of November 1, 2009, to January 31, 2010 from the number of product units distributed in the United States.

Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1. The majority of patients taking ULTRASE Capsules for the correction of steatorrhea are cystic fibrosis patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally are between the 20th and 40th percentile for weight.

2. Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts (Set 1) for males and females between the ages of 2-20 years.

   (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201).

   A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supple-mentation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from ULTRASE Capsule supple-mentation was assumed for calculation purposes.

3. It was assumed that patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for ULTRASE MT12, ULTRASE MT18, and ULTRASE MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. The table below lists unit sales information for ULTRASE MT Capsules in the United States as well as the calculation of patient-exposure-years from November 1, 2009, to January 31, 2010.

Table 3. Unit Sales of ULTRASE® MT Capsules (November 1, 2009, to January 31, 2010) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment	188,712	137,338	467,218	434,007
Number of years of treatment	517	376	1,280	1,189
Total number of patient-treatment-years	3,362			

(Table above is taken from Page 8 of the NDA 22-222 Safety Update dated March 9, 2010.)

The estimate of the patient exposure during the 3-month reported period is 3,362 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

LITERATURE UPDATE

No new relevant safety information pertaining to ULTRASE or other formulations of pancreatic enzyme preparations was noted in a search of medical literature for the periods from November 1, 2009, to January 31, 2010, as noted in the Safety Update Report dated March 9, 2010.

SUMMARY/CONCLUSION

The limited safety information submitted in the Safety Update Report covering the period from November 1, 2009, to January 31, 2010, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE capsules during the reporting period were (b) (4) capsules. Patient exposure to ULTRASE was estimated to be 3,362 "patient treatment years".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

ALI NIAK
04/30/2010

ANIL K RAJPAL
04/30/2010
I concur with Dr. Niak.

Medical Officer's Review of Safety Update Report

NDA #:	22-222
Applicant:	Axcan Pharma US, Inc.
Product:	ULTRASE® MT / ULTRASE
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted/Received:	November 5, 2009
PDUFA Date:	May 5, 2010
Date of Review:	March 16, 2010
Clinical Reviewer:	Ali Niak, M.D., Medical Officer, DGP
Through:	Anil Rajpal, M.D., Acting Team Leader, DGP

BACKGROUND

ULTRASE® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been available on the United States (US) market since November 1991. Axcan Pharma Inc. has been marketing ULTRASE® MT Capsules since August 1999 in the US. In addition, ULTRASE® is currently marketed in Canada, Argentina, Brazil and Chile.

SAFETY UPDATES

Two safety updates were submitted by the Applicant (August 4, 2009, and November 4, 2009).

The first Safety Update covered the period from November 1, 2008, to May 31, 2009, for post-marketing information, and from October 1, 2008 to May 31, 2009, for clinical study information.

The second Safety Update covered the period from June 1, 2009, through November 3, 2009 for post-marketing information, and from June 1, 2009, to November 3, 2009, for clinical study information.

Pertinent findings from both Safety Updates are presented below.

Completed Clinical Study Update

Study UMT20CF07-01 is a multicenter, open-label, Phase 3 trial designed to establish the efficacy and safety of ULTRASE® MT20 (enteric coated with HP-55, the formulation currently on the market) in cystic fibrosis children aged 7-11 years old, with presence of pancreatic insufficiency. A total of 8 patients were initially planned to be enrolled with the expectation that approximately 5 patients would complete the study. The initial protocol was submitted to IND 41,387 on May 7, 2007 (Serial 070). Subsequently, the protocol was amended to include clarifications and minor editorial changes (Protocol Amendment – Serial 075, dated June 22, 2007). No further changes were made to the amended protocol dated June 22, 2007.

This study was initiated on July 28, 2007, in the US. At study completion in March 2008, 9 patients were screened; 7 patients were included in the Intent-To-Treat (ITT) population, and 3 were included in the Per Protocol (PP) Population. The PP Population included patients for whom both inpatient periods (washout and treatment phases) were completed, all bowel movements were collected and no major protocol violations occurred. The database was locked on May 30, 2008, and the data was analyzed by (b) (4) The results obtained from the statistical analysis became available on June 20, 2008. The clinical study report for this study was completed and approved on March 2, 2009.

The demographics and status of patients at the end of study are provided in Table 1 below.

Table 1. Demographics and status of patients enrolled in study UMT20CF07-01.

Subject No.	Gender	Ethnicity	Age (years)	BMI	PATIENT STATUS
0201	Male	Caucasian	11.5	17.2	Study completed
0202	Male	Caucasian	11.5	18.5	Study completed
0301	Male	Caucasian	11.5	15.9	Study completed
0302	Male	Caucasian	10.9	14.4	Study completed
0303	Male	Caucasian	11.4	15.8	Discontinued
0401	Male	Caucasian	7.6	15.1	Discontinued
0402	Male	Caucasian	10.0	17.6	Study completed
0403	Male	African	11.1	18.6	Study completed
0404	Male	Caucasian	7.6	14.6	Study completed

(Table above is taken from Page 5 of the NDA 22-222 Safety Update dated December 9, 2008.)

No patient died or experienced serious adverse events during this clinical study. Two patients (#0303 and #0401) did not complete the study because of adverse events.

Patient #0303 developed sinusitis and was treated with antibiotics and patient #0401 developed a Streptococcal throat infection and was treated accordingly with antibiotics as well. The above two events do not appear to have been related to ULTRASE®.

Ongoing Clinical Study Update

Study UMT12CF08-01 is a multicenter, Phase IIIb open label study designed to establish the efficacy and safety of ULTRASE® MT12 in the control of steatorrhea in cystic fibrosis (CF) children with pancreatic insufficiency aged 2-6 years old. Approximately 50 patients will be enrolled in the study to obtain 40 completed patients. Initial drafts of the protocol were submitted to IND 41,387 on April 29, 2008 and November 11, 2008. Based on Agency feedback, the protocol was amended to include clarifications on the high fat diet, to better define "optimized dose" of lipase to be used, and to provide the objective criteria that would be used to determine this "optimized dose." This was done in order to not exceed the current Cystic Fibrosis Foundation guideline for maximum dosing to minimize the risk of fibrosing colonopathy. The protocol was formally submitted to IND 41,387 on March 24, 2009.

The enrolment of patients was started in April 2009 and was completed on September 25, 2009. Fifty-three patients were enrolled and as of October 30, 2009, 40 of these patients were completed.

ADVERSE EVENTS

Completed Clinical Study Update

Between 01-Nov-2008 and 31-May-2009, Axcan Pharma Inc. and its subsidiaries received 25 initial adverse event reports including a total of 46 adverse events. From these initial reports, 11 involved ULTRASE®, 12 involved VIOKASE® and 2 involved PANZYTRAT®. One initial adverse event report received during the reporting period was assessed as serious and involved VIOKASE®.

One case of product commingling, feeling abnormal, loss of consciousness, cardio-respiratory arrest and drug screen positive for methadone was reported in a 47 year-old female patient treated with VIOKASE® 16 (pancrelipase) for chronic pancreatitis. This report has not been medically confirmed. The patient had been taking VIOKASE® for many years without any problem and experienced the above mentioned adverse events after taking one pill found in a VIOKASE® bottle with a different appearance which was later identified as clarithromycin. The patient recovered and continued taking VIOKASE® without any adverse event. A potential product commingling (clarithromycin pills in VIOKASE® bottle) at the manufacturing, packaging and dispensing (pharmacy) levels was ruled out.

The adverse events of all 3 products from November 1, 2008, to May 31, 2009, are summarized in Table 2.

Table 2. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from November 1, 2008, to May 31, 2009.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Cardiac disorders				
Cardio-respiratory arrest	0	1	0	1
Gastrointestinal disorders				
Abdominal pain	0	2	0	2
Abdominal pain upper	1	1	1	3
Abnormal faeces	0	1	0	1
Diarrhoea	1	3	1	5
Dyspepsia	0	1	0	1
Faecal volume increased	1	0	0	1
Frequent bowel movements	1	0	0	1
Gastritis	0	1	0	1
Glossodynia	0	1	0	1
Groin pain	0	1	0	1
Lip swelling	0	1	0	1
Nausea	0	1	1	2
Oral discomfort	0	1	0	1
Steatorrhoea	1	0	0	1
Swollen tongue	0	1	0	1
Tongue ulceration	0	1	0	1
Vomiting	0	0	1	1
General disorders and administration site conditions				
Asthenia	0	1	0	1
Drug effect decreased	1	0	0	1
Drug ineffective	4	0	0	4
Feeling abnormal	0	1	0	1
Product commingling	0	1	0	1
Therapeutic response decreased	0	1	0	1

Coded with MedDRA dictionary

(Table above is taken from Page 8 of the Safety Update for NDA 22-222 dated August 4, 2009.)

Table 2 (Continued)

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Injury, poisoning and procedural complications				
Incorrect dose administered	0	1	0	1
Investigations				
Blood glucose increased	1	0	0	1
Blood sodium decreased	0	1	0	1
Blood sugar level fluctuation	0	1	0	1
Drug screen positive	0	1	0	1
Weight decreased	1	0	0	1
Metabolism and nutrition disorders				
Diabetes mellitus	1	0	0	1
Nervous system disorders				
Loss of consciousness	0	1	0	1
Respiratory, thoracic and mediastinal disorders				
Throat irritation	0	1	0	1
Skin and subcutaneous tissue disorders				
Rash macular	0	1	0	1
Urticaria	0	1	0	1

Coded with MedDRA dictionary

(The table above is taken from Page 9 of the NDA 22-222 Safety Update dated August 4, 2009.)

Table 2 presents the adverse events of all three products recorded in the database classified by body system (MedDRA standard organ system classification scheme (SOC)) during the period from November 1, 2008, to May 31, 2009.

For ULTRASE, the most frequently reported adverse event was drug ineffectiveness (4). The remaining adverse events were single occurrences. Please refer to Table 2.

Ongoing Clinical Study Update

Between June 1, 2009, and November 3, 2009, Axcan Pharma Inc. and its subsidiaries received 26 initial adverse event reports including a total of 45 adverse events. From these initial reports, 21 involved ULTRASE®, 4 involved VIOKASE®, and 1 involved PANZYTRAT®. Of the 26 initial adverse event reports received during the reporting period, 1 involving ULTRASE MT20 was assessed as serious and is described below.

One case of ischemic colitis (manifested as thickening and ulcers in descending colon) was reported in 71 year-old female patient who was prescribed ULTRASE MT20 (pancrelipase) for an unknown indication. The case was medically confirmed. The causal relationship between the medicinal product and the reported event is not assessable, due to the lack of information regarding the indication of use, medical history and concurrent conditions, concomitant medication and therapy dates. However, the reporting physician considered the event to be possibly related to ULTRASE MT20.

Table 3 presents the adverse events of all three products recorded in the database classified by body system (MedDRA standard organ system classification scheme (SOC)) during the period from June 1, 2009, to November 3, 2009.

Table 3. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from June 1, 2009 to November 3, 2009.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Gastrointestinal disorders				
Abdominal discomfort	1	0	0	1
Abdominal distension	2	0	0	2
Abdominal pain	1	0	0	1
Abnormal faeces	2	0	0	2
Bowel movement irregularity	1	0	0	1
Colitis ischaemic	1	0	0	1
Diarrhoea	5	0	0	5
Dyspepsia	1	0	0	1
Flatulence	1	0	0	1
Frequent bowel movement	4	0	0	4
Gastrointestinal disorder	1	0	0	1
Gastrointestinal pain	1	1	0	2
Glossodynia	1	0	0	1
Malabsorption	2	0	0	2
Oral discomfort	1	0	0	1
Paraesthesia oral	1	0	0	1
Steatorrhoea	2	0	0	2
Vomiting	1	0	0	1
General disorders and administration site conditions				
Chest pain	1	0	0	1
Drug ineffective	2	1	0	3
Feeling abnormal	1	0	0	1
Malaise	0	1	0	1

(Table above is taken from Page 6 of the NDA 22-222 Safety Update dated November 4, 2009.)

Table 3 (continued)

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Investigations				
Blood glucose fluctuation	1	0	0	1
Blood glucose increased	1	0	0	1
Blood pressure increased	0	1	0	1
Haemoglobin urine present	0	0	1	1
Metabolism and nutrition disorders				
Increased appetite	1	0	0	1
Musculoskeletal and connective tissue disorders				
Back pain	1	0	0	1
Joint swelling	0	1	0	1
Skin and subcutaneous tissue disorders				
Night sweats	0	1	0	1
Pruritus generalised	1	0	0	1
Total	38	6	1	45

Coded with MedDRA dictionary

(Table above is taken from Page 7 of the NDA 22-222 Safety Update dated November 4, 2009.)

For ULTRASE, the most frequently reported adverse events were diarrhea (5), frequent bowel movement (4), abdominal distention (2), abnormal feces (2), malabsorption (2), steatorrhea (2), and drug ineffectiveness (2). The remaining adverse events were single occurrences. Please refer to Table 3.

The above adverse events may have been related to ULTRASE, to a class effect, to the underlying condition of exocrine pancreatic insufficiency. Contamination of the drug substance with *Bacillus cereus* and/or enterotoxin cannot be ruled out as a possible etiology for the adverse events reported; contamination of the drug substance was raised as a concern on inspection of the drug substance manufacturing facility ([redacted] (b) (4) DMF # [redacted] (b) (4) (See also Consult Review from Division of Anti-infective and Ophthalmology Products [DAIOP] by Benjamin Lorenz dated June 5, 2009 and Health Hazard Evaluation by Anil Rajpal dated February 23, 2010.)

CUMULATIVE SALES AND EXPOSURE

An estimate of the patient exposure to ULTRASE Capsules was calculated for the periods of October 1, 2008, to May 31, 2009, and June 1, 2009, to November 3, 2009, from the number of product units distributed worldwide.

Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1. The majority of patients taking ULTRASE Capsules for the correction of steatorrhea are cystic fibrosis patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally are between the 20th and 40th percentile for weight.

2. Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts (Set 1) for males and females between the ages of 2-20 years.

   (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201).

   A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supplementation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from ULTRASE Capsule supplementation was assumed for calculation purposes.

3. It was assumed that patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for ULTRASE MT12, ULTRASE MT18, and ULTRASE MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. Table 4 lists unit sales information for ULTRASE MT Capsules worldwide as well as the calculation of patient-exposure-years from October 1, 2008, to May 31, 2009. Table 5 lists unit sales information for ULTRASE MT Capsules worldwide as well as the calculation of patient-exposure-years from June 1, 2009, to November 3, 2009.

Table 4. Unit Sales of ULTRASE® MT Capsules (October 1, 2008, to May 31, 2009) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment	290,068	357,688	916,606	943,768
Number of years of treatment	795	980	2,511	2,586
Total number of patient treatment years	6,872			

(Table above is taken from Page 11 of the NDA 22-222 Safety Update dated August 4, 2009.)

The estimate of the patient exposure during the 9-month reported period is 6,872 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

Table 5. Unit Sales of ULTRASE® MT Capsules (June 1, 2009, to November 3, 2009) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment	274,665	196,726	601,387	569,894
Number of years of treatment	753	539	1,648	1,561
Total number of patient treatment years	4,501			

(Table above is taken from Page 8 of the NDA 22-222 Safety Update dated November 4, 2009.)

The estimate of the patient exposure during the 5-month period is 4,501 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

LITERATURE UPDATE

No new relevant safety information pertaining to ULTRASE or other formulations of pancreatic enzyme preparations was noted in a search of medical literature for the periods from November 1, 2008, to May 31, 2009, as noted in the Safety Update Report dated August 4, 2009.

In the Safety Update Report dated November 4, 2009, seven articles were cited and discussed. These are summarized below:

- In a study on patients with diarrhea-predominant irritable bowel syndrome (D-IBS), Leeds et al.[1] detected pancreatic exocrine insufficiency in 6.1% of patients who fulfilled the Rome II criteria for D-IBS. The author suggested that pancreatic enzyme therapy might reduce diarrhea and abdominal pain in these patients, and that exocrine pancreatic insufficiency should be considered in patients with D-IBS. This reviewer believes that further studies are required to support or refute these novel observations.

[1] Leeds JS, Hopper AD, Sidhu R, Simmonette A, Azadbakht N, Hoggard N, Morley S and Sanders DS. Some Patients with Irritable Bowel Syndrome may have Exocrine Pancreatic Insufficiency. Clinical Gastroenterol and Hepatol. (2009). doi: 10.1016/j.cgh.2009.09.032.

- Wooldridge et al.[2] described the results of two studies of Zenpep for the treatment of cystic fibrosis (CF) patients with exocrine pancreatic insufficiency (EPI). It should be noted that Zenpep was recently approved (August 27, 2009) under NDA 22-210.
- In a meta-analysis by Waljee et al.[3], the efficacy and safety of pancreatic enzyme supplementation in chronic pancreatitis patients with steatorrhea is discussed. The author concludes that published trials show that: (1) enzyme supplementation improves CFA compared to placebo (although fat malabsorption is still present after enzyme supplementation); (2) stool frequency and consistency improve with supplementation (although no data on weight gain/loss are provided and minimal data on adverse events are available); and (3) Direct comparisons about the efficacy of different agents cannot be performed and insufficient data are available to determine optimal pancreatic enzyme supplementation (because important differences in patient population, pancreatic enzyme dosage and quantification of steatorrhea were present across trials and no head-to-head trials of different enzyme supplements have been performed).
- Trapnell et al.[4] described the results of a study of Creon for the treatment of CF patients with EPI. It should be noted that Creon was recently approved (April 30, 2009) under NDA 20-725.
- Munck et al.[5] described results of a cross-over study conducted in France of two formulations of "Creon"; it should be noted that the formulation and dosage strengths of "Creon" described in the article may not be the same as the currently approved Creon available in the US. One formulation was "Creon for children" (a preparation provided as a bulk of minimicrospheres in a glass container, with a small spoon containing 5000 lipase units per scoop); the other formulation was a capsule of "Creon 10,000." The author concluded that the proportion of patients with adverse experiences was comparable between groups. Three patients in the "Creon for Children" group experienced related treatment emergent adverse events (abdominal pain, constipation, vomiting) and one patient in the "Creon 10,000" group (severe diaper dermatitis). Two serious adverse events (SAEs) were observed; both considered unrelated to study medication: a bronchial obstruction and acute otitis during "Creon 10,000" treatment, and *Pseudomonas aeruginosa* colonization while receiving "Creon for Children". A toddler was prematurely withdrawn after six days of "Creon for Children;" he experienced moderate abdominal pain and diarrhea

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[2] Wooldridge JL, Heubi JE, Amaro-Galvez R, Boas SR, Blake KV, Nasr SZ, Chatfield B, McColley SA, Woo MS, Hardy KA, Kravitz RM, Straforini C, Anelli M and Lee C. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency, J Cyst Fibros (2009). doi:10.1016/j.jcf.2009.07.006

[3] Waljee AK, Dimagno MJ, Wu BU, Schoenfeld PS and Conwell DL. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. Aliment Pharmacol Ther (2009) 29 (3): 235–246.

[4] Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K and Caras S. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis, J Cyst Fibros (2009), doi:10.1016/j.jcf.2009.08.008.

[5] Munck A., Duhamel J.F., Lamireau T., Le Luyer B., Le Tallec C, Bellon G, Roussey M, Foucaud P, Giniès JL, Houzel A, Marguet C, Guillot M, David V, Kapel N, Dyard F and Henniges F. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cyst Fibros (2009) 8(1) : 14–18.

(possibly related to study medication) and vomiting (unlikely related to study medication).

- Colombo et al.[6] describes a study of twelve CF patients younger than 24 months with EPI (CFA less than 70%) treated with a formulation of "Creon for children" for 8 weeks. The author concluded that the treatment was well tolerated and significantly decreased fat malabsorption. None of the treatment emergent adverse events (TEAEs) were serious, led to death, or required discontinuation of the treatment or study. Adverse events reported for more than 2 patients were fever (4 patients, 33%) and cough (3 patients, 25%). The only treatment-related TEAE was constipation, reported for 2 patients (16.7%).
- In a meta-analysis, Taylor et al.[7] concluded that pancreatic enzyme supplements appear to improve fat malabsorption; no specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with EPI.

This reviewer concludes that there were no new significant safety findings pertaining to ULTRASE or other formulations of pancreatic enzyme preparations based on the above literature review.

SUMMARY/CONCLUSION

The limited safety information submitted in the Safety Update Report covering the periods from October 1, 2008, to May 31, 2009, and from June 1, 2009, to November 3, 2009, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE capsules during the two reporting periods (October 1, 2008, to May 31, 2009, and June 1, 2009, to November 3, 2009) were (b) (4) capsules, respectively. Patient exposure to ULTRASE was estimated to be between 6,872 (October 1, 2008, to May 31, 2009) and 4,501 (June 1, 2009, to November 3, 2009) "patient treatment years".

[6] Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, Longo L and D'Orazio C. Efficacy and Tolerability of Creon for Children in Infants and Toddlers With Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis. An Open-Label, Single-Arm, Multicenter Study. Pancreas (August 2009) 38(6): 693-699.

[7] Taylor JR, Gardner TB, Waljee AK, Dimagno MJ and Schoenfeld PS. Systematic review: efficacy and safety of pancreatic enzyme supplements for exocrine pancreatic insufficiency. Aliment Pharmacol Ther. (2009) doi: 10.1111/j.1365-2036.2009.04157.x

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

ALI NIAK
03/18/2010

ANIL K RAJPAL
03/18/2010
I concur with Dr. Niak.

MEMORANDUM

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

DATE: September 9, 2009

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022222 Ultrase (pancrelipase, USP) Capsules
Axcan Pharma US, Inc.

Summary

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

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

Dosing

Ultrase (pancrelipase, USP) Capsules is dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Ultrase should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. If approved, product labeling will specify dosing recommendations for infants up to 12 months of age, for children 1-4 years of age, and for patients 4 years of age and older. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

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

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[1] Ultrase has been marketed in the US since 1991. The to-be-marketed product is the same formulation as the currently marketed formulation.

Regulatory History[2]

Axcan Pharma US, Inc. (formerly Axcan Scandipharm, Inc.) submitted NDA 022222 on September 28, 2007, received on October 1, 2007, and was granted a priority review. A major amendment extended the review clock to July 1, 2008. FDA issued an approvable action due to unresolved chemistry, manufacturing, and controls deficiencies. A complete response was submitted on April 7, 2009, and a proposed REMS on June 2, 2009.

Concurrent with this review, FDA has reviewed submissions to DMF # (b) (4) from the drug substance manufacturer, (b) (4) ((b) (4) and to DMF #15681 from the drug product manufacturer, Eurand S.p.A, which support this NDA. Inspection of (b) (4) on (b) (4) identified numerous deficiencies that were described in a 483 that was issued on (b) (4). Based on these findings, the Office of Compliance has recommended withholding NDA approval. Re-inspection of this facility will be required before NDA 022222 may be approved. Inspection of the Eurand manufacturing facility is scheduled for September 14, 2009.

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

Chemistry, Manufacturing and Controls Considerations

Axcan Pharma US, Inc. intends to market three formulations of Ultrase capsules: MT-12, MT-18, and MT-20 containing 13,800, 20,700, and 23,000 USP units of lipase, respectively. The capsules contain identical small enteric-coated minitablets of (b) (4) pancreatic enzymes (lipase, amylase and pancrease). The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5. Stability studies of the minitablets mixed in foods (e.g., applesauce, pudding, yogurt) support the use of various foods to administer the tablets.

Drug substance ((b) (4) The drug substance, DS 1286, is (b) (4) DS 1208.[3] Several deficiencies regarding chemistry, manufacturing, and controls for the drug substance have been identified that preclude approval of the NDA. These involve concerns about the capacity of the manufacturing process to clear viruses and monitor viral load (risk mitigation plan for adventitious agents, viral inactivation studies, validation of viral infectivity assays, and specifications for adventitious agents), and several additional deficiencies including, (b) (4) process validation for DS 1208, in-process lipase activity and microbial limits acceptance criteria, DS 1286 release testing, expiry for DS 1286 and others. The (b) (4) facility inspection identified (b) (4) deficiencies that (b) (4) will have to address involving (b) (4) Drug substance deficiencies will be conveyed directly to (b) (4)

Bulk drug product (Eurand). Several deficiencies regarding chemistry, manufacturing, and controls for the bulk drug product have been identified that preclude approval of the NDA. Eurand will have to address deficiencies involving release and acceptance criteria, and provide stability data collected using the updated stability testing program. Inspection of the Eurand manufacturing facility is scheduled for September 14, 2009. Bulk drug product deficiencies will be conveyed directly to Eurand.

Packaged finished product (Axcan Pharma US, Inc). Several deficiencies regarding chemistry, manufacturing, and controls for the packaged finished product have been identified that preclude approval of the NDA. Deficiencies regarding stability of the packaged finished product, including the need for data on the stability of the product once the final container is opened by the pharmacist or patient will be communicated in the complete response letter to Axcan Pharma US, Inc. In addition, the stability data

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[2] Additional details about the review of this NDA may be found in the review by Dr. Daniel Shames dated July 1, 2008.

[3] In contrast, (b) (4)

provided for the 12-count bottle only support a 12 month expiry; additional data are needed to support the requested 16 month expiry.

Clinical Pharmacology

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

Efficacy

As with other PEP manufacturers, Axcan Pharma US, Inc., was requested to perform at least one controlled clinical trial with Ultrase to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.[4] Axcan Pharma US, Inc. conducted one clinical trial with Ultrase MT-20.

The short-term safety and efficacy of Ultrase was evaluated in a double-blind, placebo-controlled crossover trial in 31 patients, aged 8-37 years (14 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Ultrase or placebo for 6-7 days, followed by crossover to the alternate treatment for an additional 6-7 days. All patients consumed a high fat diet. Ultrase treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ($p<0.001$).

Safety

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

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of pancreatic enzyme products, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution. Patients receiving doses higher than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range. If approved, a Medication Guide will be required as part of a REMS for Ultrase that will inform patients of this risk.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Ultrase is not retained in the mouth. Ultrase should not be crushed or chewed since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

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

[4] See http://www.fda.gov/cder/guidance/6275fnl htm

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

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

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

Tradename Review

On June 10, 2009, the Division of Medication Error Prevention and Analysis (DMEPA) informed Axcan Pharma US, Inc. that the tradenames "Ultrase MT-12", "Ultrase MT-18", and "Ultrase MT-20" are not acceptable. First, the proposed suffixes, MT-12, MT-18, and MT-20, are ambiguous in their meaning and vulnerable to misinterpretation. Second, the last three letters of the proposed proprietary name Ultrase contains the US Adopted Name (USAN) stem "-ase". The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. Therefore, USAN stems should not be incorporated into proprietary names. On July 7, 2009, the applicant submitted a different proprietary name for consideration. DMEPA will conclude its review on October 5, 2009.

Pediatric Considerations

Pediatric Use. If approved, the **Use in Special Populations** section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Ultrase were demonstrated. In addition, the label will state that "The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience."

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

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

At the time of approval, FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Postmarketing Requirements under 505(o)

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

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

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

Therefore, based on appropriate scientific data, FDA has determined that Axcan Pharma US, Inc., is required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultrase in the US and to assess potential risk factors for the event.

2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Ultrase.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

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

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

Axcan Pharma US, Inc.'s proposed REMS, submitted on June 2, 2009, will need to be analogous to REMS for other porcine-derived PEPs, and will consist of a Medication Guide and a timetable for submission of assessments of the REMS. FDA's review of the proposed REMS has been deferred to the next review cycle.

_____

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

JULIE G BEITZ
09/09/2009

Cross-Discipline Team Leader Review

Date	September 9, 2009
From	Anil Rajpal, MD, Acting Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-222
Applicant	Axcan Pharma US, Inc.
Date of Submission	April 7, 2009
PDUFA Goal Date	October 7, 2009
Proprietary Name / Established (USAN) names	Ultrase® pancrelipase
Dosage forms / Strength	Ultrase® (pancrelipase) delayed release-capsules for oral administration, in USP units ▪ Ultrase 13,800 lipase/27,600 protease/27,600 amylase ▪ Ultrase 20,700 lipase/41,400 protease/41,400 amylase ▪ Ultrase 23,000 lipase/46,000 protease/46,000 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Recommended Action:	Complete Response (CR) under 21 CFR 314

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1. Introduction

This resubmission, received April 7, 2009, is a complete response to the Approvable (AE) Letter sent by the Division on July 1, 2008, and represents the second review cycle for Ultrase (pancrelipase), an enteric-coated, delayed-release pancreatic enzyme product (PEP); Ultrase is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

In the first review cycle, deficiencies were identified by the Chemistry, Manufacturing, and Controls (CMC) discipline. CMC deficiencies in the AE letter were related to: (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); (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.

No clinical deficiencies were identified in the first review cycle. The initial submission included results from a clinical study using the To be Marketed Product (TbMP): pivotal study (UMT20CF05-01; CF-01; randomized double-blind cross-over study; n=31). The current submission contains a clinical study safety update to September 30, 2008, and a postmarketing safety update to October 31, 2008. It should be noted that the TbMP is the same formulation as the current Commercially Marketed Product (CMP).

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

2. Background

2.1 Clinical Background

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

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause. Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

Fibrosing colonopathy (FC) is an important safety concern regarding PEP use. Although the etiology of FC is not known with certainty, FC has been associated with high dose PEP

exposure. Consensus guidelines have been established by the CFF in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[1,2,3] (See also Section 8 and Appendix 1.)

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

Approved PEPs: Only three PEPs have been approved under NDA to date:
(1) Cotazym (NDA 20-580): approved in 1996; not currently marketed
(2) Creon (NDA 20-725): approved in April 30, 2009
(3) Zenpep (NDA 22-210): approved August 27, 2009
Thus, there are only two approved PEPs, Creon and Zenpep, that are currently commercially available in the US.

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

Federal Register Notices: Over the past many years, the FDA has published a number of notices in the Federal Register (FR) with the aim of requiring all marketed PEPs to have undergone the NDA application and review process. This is largely to address variations in formulation, dosage, and manufacturing processes, both between different PEPs and within individual PEP brands. Recent FR notices for PEPs are summarized in the table below; a more complete history is provided in the review by Dr. Anne Pariser dated July 1, 2008.

Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products

Year	Federal Register Notices
April 1995	Notice of Final Rule: All PEPs must obtain FDA approval under NDA in order to remain on the market.
April 2004	Notice of Requirement for NDA Approval: All PEPs must obtain NDA approval within the next four years (deadline April 28, 2008)
October 2007	Notice of Extension: FDA would use enforcement discretion for the PEPs. In order to continue marketing their products, manufacturers must have: ▪ open IND by April 28, 2008, ▪ NDA submitted by April 28, 2009, and ▪ approved NDA by April 28, 2010.

Above is summarized from Anne Pariser's CDTL review dated July 1, 2008.

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

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

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

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

(2) Risk of Transmission of Viral Disease to Patients: There is a concern that because Creon, Zenpep, and other PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[4,5] To address the concern about the theoretical risk of viral transmission, a Medication Guide that informs patients of the theoretical risk of viral transmission is part of the REMS for Creon and for Zenpep. (See also Sections 3.1.1 and 3.2.1.)

2.2.2 Regulatory History of Ultrase

The table below summarizes the regulatory activity of Ultrase for EPI; a more complete summary of the period before the Approvable Action is provided in the review by Dr. Anne Pariser dated July 1, 2008.

Table 2. Pertinent Regulatory History of Ultrase

Date	Action
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
July 2008	Approvable Action
September 2008	Meeting with the Sponsor to discuss items in the Division's Approvable Letter
April 2009	Class II Resubmission – Complete Response to Approvable Letter

* IND 41387

History prior to approvable action summarized from Anne Pariser's CDTL review dated July 1, 2008.

It should also be noted that Ultrase has been commercially available in the US since 1991; it is marketed under the name "Ultrase." The current CMP formulation has been on the market since 2003. The current CMP and the TbMP are the same formulation.

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

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

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

- Cross Discipline Team Leader Review by Anne Pariser, dated July 1, 2008
- Clinical Review by Joanna Ku, dated July 1, 2008
- Statistical Review by Stella Grosser, dated June 25, 2008

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

- 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)

2.3 Current Submission

The NDA resubmission was received on April 7, 2009. It was classified as a six-month resubmission with a PDUFA deadline of October 7, 2009.

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 Ali Niak, dated September 9, 2009
(2) Clinical Pharmacology Review by Lucy Fang, dated September 8, 2009
(3) CMC Reviews from Division of Therapeutic Proteins (DTP):
   (a) Final Product Release and Packaging Issues (NDA 22-222) Review by Wei Guo, dated September 9, 2009
   (b) Drug Product (DMF 15681) Draft Review by Wei Guo, dated September 9, 2009
   (c) Drug Substance Non-Viral Issues (DMF (b) (4) Draft Review by Wei Guo, dated September 9, 2009
   (d) Drug Substance Viral Issues (DMF (b) (4) Review by Howard Anderson (DTP), dated September 2, 2009
(4) Microbiology Review (DMF (b) (4) by Stephen Langille, dated August 23, 2009
(5) Labeling Memo by Kathleen Klemm (Division of Drug Marketing, Advertising, and Communications [DDMAC]) dated September 3, 2009

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

- Proprietary Name Denied Letter sent to Axcan Pharma US, Inc. (c/o CanReg, Inc.) dated June 10, 2009 (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 Review dated July 1, 2008, for the initial review cycle, as well as to the primary review documents from that cycle.

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

3. CMC

The reader is referred to the CDTL Review by Anne Pariser dated July 1, 2008, the Final Product Release and Packaging (NDA 22-222) Review by Wei Guo dated September 9, 2009, the Drug Product (DMF 15681) Draft Review by Wei Guo dated September 9, 2009, the Drug Substance Non-Viral Issues (DMF (b) (4) Draft Review by Wei Guo dated September 9, 2009, the Drug Substance Viral Issues (DMF (b) (4) Review by Howard Anderson dated September 2, 2009, and the Microbiology Review (DMF (b) (4) by Stephen Langille dated August 27, 2009, for complete information.

Overview of Drug Substance (DS): The DS is manufactured by (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) The glands are (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b) (4) (b) (4) (b) (4) and (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) ((b) (4) and (b) (4) steps. To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

Overview of Drug Product (DP): The DP is manufactured by Eurand, the drug product Drug Master File (DMF) holder (DMF #15681), in a process that entails (b) (4) (into hard gelatin capsules). Ultrase capsules come in three strengths, Ultrase MT12, MT18, and MT20, containing 13,800, 20,700 and 23,000 USP units (U) lipase, respectively. The capsules contain identical pancrelipase formulated minitablets that are 2.0 mm in diameter. A stability study with the minitablets mixed in foods (i.e., applesauce, pudding, and yogurt) was conducted to support the use of various foods to administer the minitablets (see Section 5 Clinical Pharmacology).

Overview of Final Product Release and Packaging: Axcan Pharma US, Inc. is responsible for the final DP release and final 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

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 (b) (4) (b) (4) In response to DTP's request, (b) (4) initiated an evaluation of the (b) (4) (b) (4) and (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 EMCF 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

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) (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

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

CMC deficiencies in the 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 minitablets; (9) summary of the process validation program.

3.1.4 Final Product Release and Packaging Issues

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

Final Product Release and Packaging Issues 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 Current Review Cycle

In the current 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. (The reader is referred to the Drug Substance Non-Viral Issues Draft Review dated September 9, 2009, the Drug Product Draft Review dated September 9, 2009, the Drug Substance Viral Issues Review dated September 2, 2009, the Final Product Release and Packaging Review dated September 9, 2009, and the Microbiology Review dated August 27, 2009, for complete information.)

3.2.1 DS Viral Issues

The Viral DS Issues reviewer noted that many of the deficiencies identified in the previous cycle were adequately addressed; however, a number of deficiencies still exist that preclude approval and should be communicated to (b) (4) (See Viral Drug Substance Review by Howard Anderson dated September 2, 2009 for complete information.)

<u>Response to Deficiency Items #1 to #4</u>: A summary of Items #1 to #4 in the Deficiency Letter to (b) (4) (Control of Adventitious Viral Agents section) and a summary of the Viral DS

Issues reviewer's assessment of the adequacy of the manufacturer's response is presented below.

(1) Risk mitigation plan for adventitious agents. A deficiency should be communicated to (b) (4) the DS Viral Issues reviewer determined that two parts of this item (c and d) were not adequately addressed: (c) The concern about sanitizing/cleaning procedure was not adequately addressed as cleaning procedures were found to be grossly deficient on facilities inspection of (b) (4) (d) Similarly, the concern about cross-contamination was also not adequately addressed based on the facilities inspection results. The DS Viral Issues reviewer determined that the remaining parts (a, b, e, and f) of this item were adequately addressed: (a) The plan for disease surveillance includes a provision that glands are (b) (4) thus allowing sufficient time to prevent the release of potentially contaminated glands. (b) Information was provided by (b) (4) that the (b) (4) steps and (b) (4) steps in the manufacturing process would likely inactivate most parasites. (e) The DS Viral Issues reviewer noted that on inspection, (b) (4) indicated that pancreatic glands are obtained only from swine raised in the (b) (4); animal health certificates on file at (b) (4) were reviewed and the quality program was found to be acceptable. (f) Details of the gland qualification program were provided, and were deemed adequate by the DS Viral Issues reviewer.

(2) Viral inactivation studies. A deficiency should be communicated to (b) (4) the DS Viral Issues reviewer determined that one part of this item (a) was not adequately addressed: (a) (b) (4) provided results of viral inactivation studies using two independent experiments as requested. However, the DS Viral Issues Reviewer noted that the (b) (4) process involve (b) (4) and as would be expected does not inactivate viral agents; he recommended that (b) (4) implement an extensive viral monitoring control strategy given the limited potential of its process to reduce potential viral agents. The DS Viral Issues reviewer determined that the remaining parts (b, c, d, and e) of this item were adequately addressed: (b) (b) (4) submitted results for the inactivation of BVDV, FCV, PrV, and Reo3 for selected manufacturing steps ((b) (4) step and (b) (4) step) as requested; the DS Viral Issues Reviewer determined that the results support the viral reduction potential of each of the steps. (c) The DS Viral Issues Reviewer noted that studies of viral inactivation at lab scale were conducted under conditions appropriate to support the estimated viral reduction potential of the commercial process. (d) The DS Viral Issues Reviewer concluded that the viral infectivity procedures used for the evaluation of the (b) (4) (b) (4) (b) (4) steps were adequate, and noted that the results were likely an underestimate of the true potential of the process to inactivate viruses. (e) The DS Viral Issues Reviewer determined that there were appropriate controls to account for the potential cytotoxic effect of the PEP test article on cells and the potential interference of the PEP test article on the ability to detect virus.

(3) Validation of Viral Infectivity Assays. Critical validation parameters (e.g., specificity, robustness, limit of detection) were provided for infectious assays for a number of viruses (HEV, SVDV, PTV, EMCV, RotaA, Reo, PPV, Influenza A, VSV, and PCV2). The DS Viral Issues reviewer notes that other manufacturers ((b) (4)) had assays of comparable sensitivity, and committed to improve assay sensitivity as post-marketing

commitments. He recommends that improvement of assay sensitivity be communicated to (b) (4) in the form of a deficiency item.

(4) Specifications for Adventitious Agents. Deficiencies should be communicated to (b) (4) the DS Viral Issues reviewer determined that two parts of this item (b and d) were not adequately addressed: (b) (b) (4) was requested to estimate enveloped and non-enveloped viruses per dose of API using Q-PCR assays, to routinely monitor by Q-PCR those viruses that can potentially infect humans, and to conduct infectivity testing in selected cases where Q-PCR is positive. (b) (4) stated that this is the responsibility of the Applicant (i.e., Axcan Pharma US, Inc.; NDA 22-222). The DS Viral Issues Reviewer determined based on review of the appropriate portion of the NDA 22-222, that such procedures were not part of the NDA submission; thus, this part of the item was not adequately addressed. (d) Regarding specification for infectious PCV 1 and PCV 2, (b) (4) stated that an assay for PCV1 infectivity will be developed and implemented in approximately (b) (4) by the Applicant (Axcan Pharma US, Inc.), and that an assay for PCV2 infectivity has been developed and will be implemented in the near future; the DS Viral Issues reviewer recommends that development of an assay for PCV1 infectivity be communicated to (b) (4) as a deficiency item. The DS Viral Issues reviewer determined that the remaining parts (a and c) of this item were adequately addressed: (a) Q-PCR test results for selected viruses (HEV, EMCV, SVDV, Reo 3, Rota A, Influenza A and VSV) were provided, and were deemed adequate by the DS Viral Issues Reviewer. (c) (b) (4) eliminated (b) (4) as requested as these are not correlated with infectivity, and provided specifications for routine testing for PPV infectivity that was deemed acceptable by the DS Viral Issues Reviewer.

3.2.2 DS Non-Viral Issues

The Non-Viral DS Issues reviewer noted that a number of the deficiencies identified in the previous cycle were adequately addressed; however, a number of deficiencies still exist that preclude approval and should be communicated to (b) (4) (See Drug Substance Non-Viral Issues Draft Review by Wei Guo dated September 9, 2009 for complete information.)

DS used in Ultrase vs. (b) (4). (b) (4) is the drug substance DMF Holder for both Ultrase and (b) (4) It should be noted that the drug substance used in Ultrase (NDA 22-222) is DS 1286, a (b) (4) DS 1208 (a primary drug substance) whereas the drug substance used in (b) (4) is DS 1206 (a primary drug substance) and DS 1208 (a primary drug substance). It should be noted that some deficiencies that are also applicable to the Ultrase NDA were already communicated to (b) (4) after the review of the (b) (4) in a deficiency letter dated (b) (4).

Response to Deficiency Items #1 to #19: A summary of Items #1 to #19 in the Deficiency Letter to (b) (4) (CMC for Drug Substance section) and a summary of the Non-Viral DS reviewer's assessment of the adequacy of (b) (4) response is presented below.

(1) Amount of raw material used and limits on process-related impurities: A deficiency was identified but was already communicated to (b) (4) The amount of raw material was

not provided for the manufacturing of DS 1206, the release specifications for (b) (4) (b) (4) differed between DS 1206 and DS 1208, and forced degradation studies were not conducted to evaluate the suitability of the RP-HPLC method. This deficiency item was communicated to (b) (4) on 8/28/09.

(2) Acceptance criteria, storage conditions, and expiration date: A deficiency was identified but was already communicated to (b) (4) Although this item was adequately addressed (i.e., acceptance criteria for lipase, amylase, protease, (b) (4) content, and microbial limits, as well as storage conditions and expiration date were provided), an additional related deficiency item was identified - results of the study demonstrating equivalence of the (b) (4) were not provided. This deficiency item was communicated to (b) (4) on 8/28/09.

(3) Process data for DS 1208 and DS 1286: A deficiency should be communicated to (b) (4) Process data for DS 1208 (a primary drug substance) and DS 1286 (b) (4) were requested. For DS 1208, "alert limit" and "action limit" were provided for (b) (4) and "finished product" lipase activity. Although the alert and action limits were acceptable for (b) (4), it was not clear if "finished product" referred to DS 1286; thus, (b) (4) was sent a deficiency item on 8/28/09 requesting clarification of what is meant by "finished product." The DS Non-Viral Issues Reviewer now recommends an additional deficiency item regarding (b) (4) step process validation for DS 1208 be communicated to (b) (4)

(4) Rejected batches may not be reworked or reprocessed: This item was adequately addressed as (b) (4) stated that it does not plan to reprocess or rework rejected batches.

(5) In-process lipase activity and microbial limits acceptance criteria: A deficiency should be communicated to (b) (4) The DS Non-Viral Issues Reviewer recommends that (b) (4) provide the target lipase activity for glands used in the manufacturing of DS 1208 and DS 1206.

(6) (b) (4) characterization study: This item was adequately addressed as the final report of a protocol to characterize the excess of (b) (4) in pancreatin using olive oil as a substrate was provided for DS 1208, and was deemed acceptable by the DS Non-Viral Issues Reviewer.

(7) DS characterization for amylase: This item was adequately addressed as amylase activity was provided for 12 lots.

(8) DS 1286 release testing: A deficiency should be communicated to (b) (4) Release testing specifications for DS 1286 using a validated RP-HPLC analysis method were requested. Although release specifications (i.e., for the peak ratio of (b) (4)) were provided, (b) (4) stated that applying additional RP-HPLC peak ratio specifications to the API is not currently possible; a deficiency item was sent on 8/28/09 that (b) (4) should establish acceptance criteria for all peaks identified by RP-HPLC for DS 1206 and DS 1208. The DS Non-Viral Issues Reviewer now recommends that an additional

deficiency item be sent regarding methods and acceptance criteria for the RP-HPLC assay.

(9) Specification for (b) (4) content and impurities for release testing: (b) (4) was requested to include in its DS release specifications testing for (b) (4) content and other impurities including degradants. The DS Non-Viral Issues reviewer noted that (b) (4) and (b) (4) are the only solvents used, and that solvent specifications were provided for DS 1208 and DS 1286. He noted that RP-HPLC specifications described in response to Item 8 provide specifications of product-related substances and impurities.

(10) Tightening of protease and amylase activity acceptance criteria: Revised specifications of protease and amylase activity were provided by (b) (4) and were deemed acceptable by the DS Non-Viral Issues Reviewer.

(11) (b) (4) specification for DS release: This item was adequately addressed as described in Item 6 above.

(12) Olive oil qualification: A deficiency item was identified, but was already communicated to (b) (4) response to a request to provide characterization of the olive oil used in the lipase activity assay was not deemed adequate by the DS Non-Viral Issues Reviewer. The deficiency item was communicated to (b) (4) on 8/28/09; they were requested to monitor for critical olive oil attributes and to establish acceptance criteria for critical olive oil components.

(13) Linearity of assays (lipase, amylase, and protease): Linearity of assay methods for lipase, amylase, and protease, were provided, and were deemed acceptable by the DS Non-Viral Issues Reviewer.

(14) Demonstration of predicted activity (lipase, amylase, and protease): Method validations were provided for assays of drug substance, and were deemed acceptable by the DS Non-Viral Issues Reviewer.

(15) Validation of assays (lipase, amylase, and protease): Validation data for lipase, amylase, and protease assays were provided, and were deemed acceptable by the DS Non-Viral Issues Reviewer.

(16) Trend of stability data for DS 1208 and DS 1286: Stability data were provided for 1208 and 1286; thus, this item was adequately addressed.

(17) Expiry for DS 1208: A deficiency item was identified, but was already communicated to (b) (4) responded that the expiry for 1208 is no more that 24 months, and the hold time is up to 24 months, but supporting data were not provided. (b) (4) was sent a deficiency item on 8/28/09 to identify an expiry or hold time for 1206 and 1208 before (b) (4) along with supporting data.

(18) Expiry for DS 1286: (b) (4) responded that the expiry proposed for DS 1286 is 24 months; thus, this item was adequately addressed.

(19) DS release test sampling plan: The DS release test sampling plan was provided by (b) (4) and was deemed acceptable by the DS Non-Viral Issues Reviewer.

3.2.3 DP Issues

The DP reviewer noted that a number of the deficiencies identified in the previous cycle were adequately addressed; however, a number of deficiencies still exist that preclude approval and should be communicated to Eurand. (See Drug Product Draft Review by Wei Guo dated September 9, 2009 for complete information.)

Response to Deficiency Items #1 to #9: A summary of Items #1 to #9 in the Deficiency Letter to Eurand, and a summary of the DP reviewer's assessment of the adequacy of Eurand's response is presented below.

(1) Release and acceptance criteria: Deficiencies should be communicated to Eurand. The DP reviewer determined that two parts of this item (b and d) were not adequately addressed: (b) Specification for (b) (4) content was noted to be higher than that of (b) (4); the DP reviewer recommends that the acceptance criterion for (b) (4) content be a tightened. (d) In Eurand's release test sampling, the contents of capsules collected from different drums are mixed together; the DP reviewer recommends that the release testing sampling be updated to test capsules individually. The DP reviewer determined that the remaining parts of this item (a and c) were adequately addressed: (a) description of the HPLC validation method; and (c) acceptance criteria with a range of capsule weight.

(2) Stability data: A deficiency should be communicated to Eurand. The DP reviewer determined that one part of this item was not adequately addressed: (b) Eurand provided stability data with trend analysis on lots manufactured in 2006 and 2007 as requested; however, the DP reviewer recommends that Eurand provide stability data collected using the updated stability testing program and acceptance criteria provided in the DMF update. The DP reviewer determined that the other part of this item was adequately addressed: (a) testing for (b) (4) content, product-related substances and impurities (i.e. degradants) in the Eurand stability program.

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

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

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

(6) (b) (4) assay method: A description of the (b) (4) assay method used in the (b) (4) was provided, and was deemed acceptable by the DP reviewer.

(7) (b) (4) process: A description of the (b) (4) process used in the (b) (4) step of manufacturing was provided along with in-process controls and related acceptance criteria; this was deemed acceptable by the DP reviewer.

(8) Enteric coating: The coating of the minitablets used for this product is hypromellose phthalate (HP55). The DP reviewer noted that there are four phthalates that have been used for enteric coating of PEP products (cellulose acetate phthalate, dibutyl phthalate, diethyl phthalate and hypromellose phthalate), and that there is a potential safety concern with dibutyl phthalate as published literature indicates that it may be an endocrine disruptor. The DP reviewer confirmed that dibutyl phthalate is not used in the Ultrase product. Thus, concerns regarding this coating have been adequately addressed.

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

3.2.4 Final Product Release and Packaging Issues

The Final Product Release and Packaging Issues reviewer noted that many of the deficiencies identified in the previous cycle were adequately addressed; however, a number of deficiencies still exist that preclude approval and should be communicated to the Applicant (Axcan Pharma US, Inc.). (See Final Product Release and Packaging Review by Wei Guo dated September 9, 2009 for complete information.)

Response to Deficiency Items #2a to #2d: A summary of Items #2a to #2d in the CR Letter to the Applicant (Axcan Pharma US, Inc.), and a summary of the Final Product Release and Packaging Issues Reviewer's assessment of the adequacy of the Applicant's response is presented below.

(2a) Stability data to support 24-month expiry: A deficiency should be communicated to the Applicant. It appears that the Applicant provided stability data for pre-packaged product. The Final Product Release and Packaging Issues Reviewer recommends that the Applicant be requested to provide stability tests performed on packaged finished product.

(2b) Stability data across lots: Stability data including trend analysis were provided by dosage strength formulation (i.e., MT12, MT18, and MT20) and by packaging size (i.e.,

12 capsule, 100 capsule, or 500 capsule bottles). The results were deemed acceptable by the Final Product Release and Packaging Issues Reviewer.

(2c) Release and stability testing: A deficiency should be communicated to the Applicant. Release and stability testing for (b) (4) content, product-related substances, and impurities were provided, but these did not conform to the revised specifications. The Final Product Release and Packaging Issues Reviewer recommends that the Applicant conduct release and stability testing for (b) (4) content, product-related substances, and impurities using the revised specifications.

(2d) USP lipase reference standard used: The Applicant stated that two activities of the reference standard were due to a discrepancy between the USP label units and those reported by industry. The Final Product Release and Packaging Issues Reviewer noted that the Agency and the Applicant agreed to use a working standard. He also noted that a similar response was provided by Eurand (the Applicant for Zenpep under NDA 22-210) and that the response is acceptable.

Additional Deficiency Items: The Final Product Release and Packaging Issues Reviewer provided recommendations for additional deficiency items as follows:

- Forced degradation studies: The Final Product Release and Packaging Issues Reviewer noted that the Applicant has not addressed the stability of the product once the final container is opened by the pharmacist or by the patient. Thus, he recommends that forced degradation studies (i.e. photostability, moisture conditions, etc.) be conducted on the drug product to support in-use stability of drug product.

- Stability data: The Final Product Release and Packaging Issues Reviewer noted that the stability data provided by the Applicant for the 12 capsule bottle only support 12 months expiry. Thus, he recommends that the Applicant revise the label accordingly, or provide additional data to support the requested dating period of 16 months.

3.2.5 Microbiology Issues

DMF (b) (4) was reviewed by the Microbiology Reviewer as a result of a recent 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 that DMF (b) (4) is adequate to support NDA 22-222. However, he recommended that (b) (4) provide information on selected manufacturing processes as follows:

1. Provide the following information regarding the handling and testing of the intact pancreas glands prior to (b) (4):
    a. Are the glands washed or processed in any way prior to (b) (4)
    b. Are there microbiological acceptance criteria in place for the pancreas glands

2. Section 3.2.S.2.1.2.2 of DMF (b) (4) states that the maximum length of the pancreatin/pancrelipase manufacturing process is (b) (4)). Please provide the following information regarding the manufacturing process:
   a. A justification for this (b) (4) 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

These comments were included in a Deficiency Letter sent to (b) (4) dated August 28, 2009. Thus, no additional comments to (b) (4) are recommended from the Microbiology Discipline.

3.2.6 Other Issues

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 April to May 2009, and a FDA Form 483 with (b) (4) observations was issued. The GMP status of (b) (4) is under evaluation. Determination of GMP status will be made after review of (b) (4) response to each of the findings.

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 Final Recommendation

A Complete Response Action is the final recommendation by CMC.

Deficiency items to be communicated to the Applicant (NDA 22-222), to the drug substance DMF holder (# (b) (4) and to the drug product DMF holder (# 15681) are provided in Sections 13.1.1, 13.1.2, and 13.1.3, respectively.

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[6], given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Ultrase clinical development program. However, toxicology studies are needed if the excipients in the Ultrase 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 Ultrase 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 Ultrase.

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 Ultrase, 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 Ultrase administration, and that an approval of the Ultrase NDA is recommended.

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

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

- Indications and Usage section of Highlights: "Pancreatic enzyme preparation digestant" is recommended as the established pharmacologic class.
- 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."

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

4.2 Current Review Cycle

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

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

4.3 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline provided the labeling revisions described above are made.

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 Ultrase-Eudragit (older formulation of Ultrase coated with Eudragit) and Ultrase-TbMP (Ultrase 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), Ultrase-TbMP had higher mean percent recovery than Ultrase-Eudragit (43% vs. 27%, respectively). In CP patients (n=5), Ultrase-Eudragit had a higher mean percent recovery than Ultrase-TbMP (260% vs. 141%, respectively). Dr. Chen concluded that comparability of the two Ultrase 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 Ultrase 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 Ultrase 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 Ultrase 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 Ultrase was not recommended for Approval during the initial review cycle, labeling changes were not negotiated with the Applicant.

5.2 Current Review Cycle

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

During this 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 minitablets in Ultrase Capsules is designed to dissolve at pH ≥ 5.5 which allows delivery of the enzymes to the duodenum. However, it was shown in the *in vitro* stability study that the minitablets were stable in chocolate pudding (approximate 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., minitablets 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 100^0C 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 37^0C.
- 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 minitablet 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 Ultrase minitablets can only be mixed with acidic food (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.

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

5.3 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology discipline provided the labeling revisions described above are made.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Ultrase 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; CF-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 (Pivotal Study; Study CF-01) was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of Ultrase 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 Ultrase 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 (Ultrase TbMP → placebo), and 17 patients to treatment sequence 2 (placebo → Ultrase 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 Ultrase TbMP treatment was 89%. The difference in mean CFA on Ultrase 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

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
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	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-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 ≤40%),
- moderately-affected (>40 and ≤80%), and
- mildly-affected (>80%).

The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of ≤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 ≥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 Ultrase TbMP treatment was 89%, and the mean difference on Ultrase 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 Ultrase treatment was 87%, and the mean difference on Ultrase 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 Ultrase treatment was 92%, and the mean difference on Ultrase as compared to placebo was 3%. This difference is not 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 Ultrase treatment correlated strongly with placebo-CFA; i.e., patients with lower CFA while on placebo had the greatest increases in CFA on Ultrase 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 Ultrase that was studied in the pivotal study. In addition, there is considerable clinical experience with similar formulations of porcine-derived PEPs.

7.2 Current Review Cycle

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

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

7.3 Final Recommendation

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

8. Safety

The reader is referred to the CDTL Review by Anne Pariser dated July 1, 2008, the Clinical Review by Joanna Ku dated July 1, 2008, and the Clinical Review of Safety Update by Ali Niak, dated September 9, 2009 for complete information.

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

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

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

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

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

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.

- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g., pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.

- 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

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

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

8.1 Initial Review Cycle

The reader is referred to the CDTL Review by Anne Pariser dated 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 Ultrase as described in the individual studies was consistent with the currently described AE profile of PEPs in the medical literature. In general, AEs tended to reflect underlying disease, and were most commonly reported in the gastrointestinal (GI) and respiratory systems. There were no new or noteworthy AEs noted during the initial cycle of safety review.

8.2 Current Review Cycle

The reader is referred to the Clinical Review of Safety Update by Ali Niak, dated September 9, 2009 for complete information.

Dr. Niak 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; a literature search was also provided.

Postmarketing Experience: Dr. Niak notes that based on US unit sales of Ultrase® MT Capsules during the reporting period (December 1, 2007 through September 30, 2008), patient exposure was estimated to be approximately 7,058 patient-treatment-years. 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 30th percentile); weight was selected based on age and weight data in the Cystic Fibrosis Foundation (CFF) Registry. It should be noted that US sales of Ultrase® MT Capsules constitute the greatest percentage globally (more than (b)(4)%) although Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile and Canada). For Ultrase® MT, a total of 17 case reports of adverse events were received. Two of the case reports were serious (severe abdominal pain in a 71-year-old male, and diarrhea/abdominal discomfort in an18-month old); for each of the patients, no information was provided regarding medical history and indication. Diarrhea and abdominal pain are known to be

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

associated with EPI and have also been described in clinical trials of the two currently available approved PEPs (Zenpep and Creon). These reports may represent under-treatment; however, given the limitations of the postmarketing safety information provided (e.g., lack of information about dose, treatment duration, and co-morbid conditions) as well as general limitations of postmarketing information (e.g., difficulty estimating reporting rate and denominator), etiology cannot be determined. Nevertheless, bacterial contamination of the drug substance (see Section 3.2.6) cannot be ruled out as a possible etiology for these cases. Fifteen of the case reports were non-serious (predominantly gastrointestinal signs and symptoms and/or lack of efficacy) spontaneous reports; no information was provided regarding medical history and indication. The most frequently reported adverse events were diarrhea (5), followed by lack of efficacy (4), abdominal pain (3), erythema (3), and generalized pruritus (2). The remaining cited adverse events were single occurrences. The pattern of common adverse events appeared to be similar to that described in the labeling for the two currently available approved PEPs (Zenpep and for Creon); the clinical reviewer noted that there appeared to be more cases of diarrhea in the postmarketing reports for Ultrase than that described in the labeling for Zenpep and for Creon. However, given the limitations of the postmarketing information provided as well as the small size of the clinical trials of Creon and of Zenpep, it is not possible to draw a clear conclusion regarding relative rates of the adverse events. It should also be noted that bacterial contamination of the drug substance (see Section 3.2.6) cannot be ruled out as a possible etiology for the adverse events reported.

Clinical Study Update: A safety update to September 30, 2008, was provided for a completed study of CF patients aged 7 to 11 years old using Ultrase® MT20, the HP55 coated formulation that is the same as the CMP. Nine patients were enrolled; two patients discontinued due to AEs (one patient was an 11 year old male with sinusitis; the other patient was a 7 year old male with streptococcus pharyngitis). The investigator and the clinical reviewer deemed these AEs unrelated to Ultrase® MT.

Literature Update: The Applicant conducted a search of the medical literature for the period from December 2, 2007, to October 31, 2008. The Applicant stated that the literature search did not provide any new relevant safety information pertaining to Ultrase® MT or other formulations of pancreatic enzyme preparations.

8.3 Final Recommendation

Should Ultrase receive an Approval action during a subsequent review cycle, a Risk Evaluation and Mitigation Strategy (REMS) is recommended to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients (see Deficiency Item #6 in Section 13.1 Recommended Regulatory Action, and see Section 13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements).

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The application was not presented to the Pediatric Research Committee (PeRC) during this review cycle because Ultrase is not recommended for Approval during this review cycle. Presentation to PeRC may occur should Ultrase receive an Approval action during a subsequent review cycle.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Ultrase is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

Initial Review Cycle

In the initial review cycle, site inspections of two clinical sites 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 4. 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	Protocol violations: (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. Overall assessment: The data from this site can be used in support of the NDA.
Site 03 Steven Strausbaugh, MD Cleveland, OH	Six	Minor protocol violations: Two patients enrolled before results of fecal elastase results available; results later found to be within the protocol requirement. Overall assessment: The data from this site can be used in support of the NDA.

Information in the table above is taken from the CTDL 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.

Current Review Cycle

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

11.3 Drug Shortage

Currently, Creon and Zenpep are the only PEPs that are available on the market that have undergone the NDA review process. There are other PEPs on the market that have not undergone the NDA review process, but these will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010. The, impact of a Complete Response action for Ultrase on the possible development of a drug shortage in the near future (i.e., by April 28, 2010; the time that all marketed PEPs must have an approved NDA) is not known at the present time.

11.4 Facilities Inspection

During a recent inspection of the [redacted] (b) (4) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

12. Labeling

12.1 Proprietary name

<u>Initial Review Cycle:</u>

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 previous review cycle, no trade name had been agreed upon with the Applicant.

Current Review Cycle:

In the current 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.

It should be noted that 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 writing of this CDTL Review. (The proprietary name review is ongoing, and a decision on the name will be made prior to the PDUFA date for this NDA of October 7, 2009.)

Since Ultrase is not recommended for Approval, labeling changes will not be negotiated with the Applicant during this review cycle; the DMEPA Label and Labeling Review will be conducted and labeling changes will be planned for negotiation with the Applicant should Ultrase receive an Approval action during a subsequent review cycle.

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

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the proposed proprietary 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

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

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The CMC Reviewer (of Final Product Release and Packaging) recommends this NDA for CR because he identified a number of deficiency items in the application related to stability testing. In addition, drug product deficiencies (identified by the CMC Drug Product Reviewer) will be communicated in a separate letter to the drug product DMF Holder, Eurand (DMF 15681), and viral and non-viral drug substance deficiencies (identified by the CMC Drug Substance Viral Issues Reviewer and the CMC Drug Substance Non-Viral Issues Reviewer) will be communicated in a separate letter to the drug substance DMF Holder, (b) (4) (DMF (b) (4)

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

13.1.1 CR Letter to Axcan Pharma US, Inc. (NDA 22-222)

<u>CMC Deficiencies</u>**:**

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 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.

Clinical Deficiencies**:**

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.

7. Submit draft labeling that incorporates the revisions in the attached labeling. In addition, submit 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.

We reserve comment on the proposed carton and container labeling until the application is otherwise adequate.

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

Viral DS Deficiencies:

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

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1) to establish lot release specifications for the drug substance.

3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance release.

4. Please 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.

5. 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.

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

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

Non-Viral DS Deficiencies:

1. In regards to your RP-HPLC assay used to monitor purity of 1286, we have the following comment:

    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 folds 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

    In regards to your RP-HPLC identity assay, please provide acceptance criteria based on peak area rather than absorbance ratios.

2. The (b) (4) process of 1208 should be revalidated to include the (b) (4) time challenge. The validation of each (b) (4) should be conducted in triplicate.

3. 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 manufacturing process of 1208 and 1206.

4. Provide the method validation and final report for the RP-HPLC assay used in release and stability testing.

5. Provide samples of your drug substance label.

13.1.3 Deficiency Letter to Eurand (DMF 15681)

DP Deficiencies:

1. Please perform all release tests on capsulated product.

2. Please perform microbial limit test on every lot manufactured and 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. Please update your release testing sampling to test capsules individually.

4. The release and stability acceptance criteria set for the RP-HPLC assay are not adequate. Please establish and justify release and stability acceptance criteria for all peaks identified in the RP-HPLC.

5. Please revise your acceptance criterion for moisture content to reflect process capability and historical results.

6. Please submit stability data collected using the updated stability testing program and acceptance criteria provided in the DMF update.

13.2 Risk Benefit Assessment

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

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

See Deficiency Item #6 (in CR Letter to Axcan Pharma US, Inc.) in Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since Ultrase is not recommended for Approval during this review cycle, recommendations for postmarketing pediatric requirements such as development of an age appropriate formulation will be made should Ultrase receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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

> 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 a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients taking TRADENAME (pancrelipase) Capsules.

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

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

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

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

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

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

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

13.7 Recommended Comments to Applicant

None.

APPENDIX 1

The CFF Dosing Guidelines (from Borowitz et al., 1995[12]) 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[13] 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[14] 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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[12] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.

[13] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.

[14] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations."

APPENDIX 2

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) (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) 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 [redacted] (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 [redacted] (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

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 minitablets.

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

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 minitablets.

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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

ANIL K RAJPAL
09/09/2009

DONNA J GRIEBEL
09/09/2009

Medical Officer's Review of Safety Update Report

NDA #:	22-222
Sponsor:	Axcan Pharma US, Inc.
Product:	ULTRASE® MT / ULTRASE
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted/Received:	April 7, 2009
PDUFA Date:	October 7, 2009
Date of Review:	September 9, 2009
Clinical Reviewer:	Ali Niak, M.D., Medical Officer, DGP
Through:	Anil Rajpal, M.D., Acting Team Leader, DGP

Background

ULTRASE® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been available on the United States (US) market since November 1991. Axcan Pharma Inc. has been marketing ULTRASE® MT Capsules since August 1999 in the US. In addition, ULTRASE® is currently marketed in Canada, Argentina, Brazil and Chile.

Safety Update

A Safety Update was submitted by the Sponsor on December 9, 2008. The Safety Update covered the period from December 2, 2007 to October 31, 2008 for post-marketing information, and from December 1, 2007 to September 30, 2008 for clinical study information. Pertinent findings from the Safety Update are presented below.

Clinical Study Update

Study UMT20CF07-01 is a multicenter, open-label, Phase 3 trial designed to establish the efficacy and safety of ULTRASE® MT20 (enteric coated with HP-55, the formulation currently on the market) in cystic fibrosis children aged 7-11 years old, with presence of pancreatic insufficiency. A total of 8 patients were initially planned to be enrolled with the expectation that approximately 5 patients would complete the study. The initial protocol was submitted to IND 41,387 on May 7, 2007 (Serial 070). Subsequently, the protocol was amended to include clarifications and minor editorial changes (Protocol Amendment – Serial 075, dated June 22, 2007). No other changes were made to the amended protocol dated June 22 2007.

This study was initiated on July 28, 2007 in the US. At study completion in March 2008, 9 patients were screened; 7 patients were included in the Intent-To-Treat (ITT) population, and 5 were included in the Per Protocol (PP) Population. The PP Population included patients for whom both inpatient periods (washout and treatment phases) were completed, all bowel movements were collected and no major protocol violations occurred. The database was locked on May 30, 2008, and the data was analyzed by (b) (4) The results obtained from the statistical analysis became available on June 20, 2008. The clinical study report for this study should be completed on December 8, 2008.

The demographics and status of patients at the end of study are provided in Table 1.

Table 1. Demographics and status of patients enrolled in study UMT20CF07-01.

Subject No.	Gender	Ethnicity	Age (years)	BMI	PATIENT STATUS
0201	Male	Caucasian	11.5	17.2	Study completed
0202	Male	Caucasian	11.5	18.5	Study completed
0301	Male	Caucasian	11.5	15.9	Study completed
0302	Male	Caucasian	10.9	14.4	Study completed
0303	Male	Caucasian	11.4	15.8	Discontinued
0401	Male	Caucasian	7.6	15.1	Discontinued
0402	Male	Caucasian	10.0	17.6	Study completed
0403	Male	African	11.1	18.6	Study completed
0404	Male	Caucasian	7.6	14.6	Study completed

No patient died or experienced a serious adverse event during this clinical study. Two patients (#0303 and #0401) did not complete the study because of adverse events. Patient #0303 developed sinusitis and was treated with antibiotics and patient #0401 developed a Streptococcal throat infection and was treated accordingly with antibiotics as well. The above two events do not appear to have been related to ULTRASE®.

Adverse Events

Between December 2, 2007, and October 31, 2008, Axcan Pharma, Inc. and its subsidiaries received 41 adverse event reports including a total of 86 adverse events. From these reports, 17 involved ULTRASE®, 15 involved VIOKASE® and 9 involved pancreatin formulations (PANZYTRAT® or PANPUR®). Three of the 41 adverse event reports received during the reporting period were assessed as serious.

For ULTRASE®, a total of 17 adverse event reports was received. One serious adverse event report involved a case of severe abdominal pain (cramps) in a 71-year-old male patient who was treated with ULTRASE® for an unknown indication. The patient was hospitalized for 9 days. ULTRASE® was discontinued; however, the outcome was not reported. Another serious adverse event was reported in an 18-month old patient treated with ULTRASE® for an unknown indication. The patient was noted to be experiencing diarrhea and abdominal discomfort. The case was assessed as medically relevant. The patient was given a new bottle of ULTRASE® from a different lot and she recovered from the events. These serious adverse events may have been related to ULTRASE®, to a class effect, or to the underlying condition of exocrine pancreatic insufficiency. Bacterial contamination of the drug substance cannot be ruled out as a possible etiology for the adverse events reported; bacterial contamination of the drug substance was raised as a concern on inspection of the drug substance manufacturing facility (DMF # (b) (4) (See also Consult Review from Division of Anti-infective and Ophthalmology Products [DAIOP] by Benjamin Lorenz dated June 5, 2009.)

One fatal case of dispensing error with subsequent overdose, aspiration, atelectasis, and death was reported in a 3-week-old male infant who was treated for pancreatic insufficiency with VIOKASE® powder through a nasogastric tube. VIOKASE® is not approved for administration through nasogastric tubes.

The adverse events of all 3 products are summarized in Table 1.

For ULTRASE®, the most frequently reported adverse events were diarrhea (5), drug ineffectiveness (4), abdominal pain (3), erythema of the skin and subcutaneous tissue disorders (3), and generalized pruritus (2). The remaining cited adverse events were single occurrences. There appeared to be more cases of diarrhea in the postmarketing reports of ULTRASE® than that described in the labeling for the two available approved PEPs (Creon and Zenpep). However, the general pattern of adverse events was similar to that reported in the clinical trials of Creon and Zenpep, and is consistent with known symptoms of EPI. Please refer to Table 2.

Table 2 Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from 02-Dec-2007 to 31-Oct-2008

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT® / PANPUR®	Total
Gastrointestinal disorders				
Abdominal discomfort	1	0	2	3
Abdominal distension	0	1	1	2
Abdominal pain	3	0	0	3
Abdominal pain upper	1	0	0	1
Diarrhoea	5	2	2	9
Dyspepsia	0	1	0	1
Flatulence	1	1	0	2
Gastrooesophageal reflux disease	1	0	0	1
Glossitis	0	1	0	1
Glossodynia	0	1	0	1
Nausea	1	2	0	3
Reflux gastritis	1	0	0	1
Stomach discomfort	1	1	0	2
Tongue exfoliation	0	1	0	1
Vomiting	0	0	2	2
General disorders and administration site conditions				
Asthenia	0	2	0	2
Condition aggravated	1	0	0	1
Death	0	1	0	1
Drug ineffective	4	2	0	6
Drug ineffective for unapproved indication	1	2	0	3
Feeling jittery	1	0	0	1
Gait disturbance	0	0	1	1
Oedema peripheral	0	0	1	1
Sensation of foreign body	0	0	1	1
Therapeutic response decreased	0	1	0	1
Immune system disorders				
Hypersensitivity	0	1	1	2

Table 2 (continued)

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT® / PANPUR®	Total
Infections and infestations				
Urinary tract infection	0	1	0	1
Injury, poisoning and procedural complications				
Overdose	0	1	0	1
Investigations				
Blood glucose fluctuation	0	0	1	1
Blood sodium abnormal	0	1	0	1
Gamma-glutamyltransferase increased	0	0	1	1
Weight decreased	1	3	0	4
Metabolism and nutrition disorders				
Appetite decreased	1	0	0	1
Nervous system disorders				
Burning sensation	1	0	1	2
Disturbance in attention	0	1	0	1
Headache	0	2	0	2
Hypoaesthesia	1	0	0	1
Psychomotor hyperactivity	1	0	0	1
Syncope vasovagal	0	1	0	1
Psychiatric disorders				
Nervousness	1	0	0	1
Renal and urinary disorders				
Chromaturia	0	1	0	1
Pollakiuria	0	0	1	1
Respiratory, thoracic and mediastinal disorders				
Aspiration	0	1	0	1
Atelectasis	0	1	0	1
Nasal inflammation	1	0	0	1
Skin and subcutaneous tissue disorders				
Erythema	3	0	0	3
Pruritus	0	0	2	2
Pruritus generalized	2	0	0	2
Rash	0	1	0	1
Vascular disorders				
Flushing	1	0	0	1

Coded with MedDRA dictionary

(Obtained from NDA 22-222 ULTRASE® MT capsules Safety Update Report, Axcam Pharma U.S. Inc., Dec. 9th, 2008.

The limited adverse event data presented above are consistent with the known adverse event profile of pancreatic enzyme products (PEPs).

Cumulative sales and exposure of unbranded pancrelipase product

An estimate of the patient exposure to ULTRASE® Capsules was calculated for the period of December 1st, 2007, to September 30th, 2008, from the number of product units distributed in the U.S. While ULTRASE® Capsules are marketed in other countries (Argentina, Brazil, Chile and Canada), U.S. sales overwhelmingly constitute the greatest percentage globally (more than (b)(4)%).

Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1) The majority of patients taking ULTRASE® MT Capsules for the correction of steatorrhea are cystic fibrosis (CF) patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally sit between the 20th and 40th percentile for weight.

2) Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts (Set 1) for males and females between the ages of 2-20 years.

   (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201).

   A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supplementation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from ULTRASE® MT Capsule supplementation was assumed for calculation purposes.

3) It was assumed that patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for ULTRASE® MT12, ULTRASE® MT18 and ULTRASE® MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. Table 3 lists U.S. unit sales information for ULTRASE® MT Capsules as well as the calculation of patient-exposure-years.

Table 3 U.S. Unit Sales of ULTRASE® MT Capsules (Dec. 1st, 2007, to Sept. 30th, 2008) and Patient Exposure

	MT12 100 ct	MT18 100 ct	MT20 100 ct	MT20 500 ct
	Units	Units	Units	Units
December 1st, 2007 – September 30th, 2008	(b) (4)			
Total number of capsules				
Number of days of treatment	270,851	381,133	1,018,901	767,852
Number of years of treatment	742	1,044	2,791	2,103
Total number of patient treatment years	7,058			

(Obtained from NDA 22-222 ULTRASE® MT capsules Safety Update Report, Axcam Pharma U.S. Inc., Dec. 9th, 2008.

The estimate of the patient exposure during the 10-month reported period is approximately 7,058 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal, a total of 3 meals and 2 snacks per day, and an average weight of 54.3 kg.

Literature Update

No new relevant safety information pertaining to ULTRASE® or other formulations of pancreatic enzyme preparations was noted in a search of medical literature for the period from December 2, 2007 to October 31, 2008.

Summary/Conclusion

The limited safety information submitted in the Safety Update Report covering the period of December 2, 2007, to September 31, 2008, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE® MT capsules during the reporting period were (b) (4) capsules. Patient exposure to ULTRASE® MT was estimated to be between 7,058 "patient treatment years".

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22222	ORIG 1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

ALI NIAK
09/09/2009

ANIL K RAJPAL
09/09/2009

Memorandum

RE: 22-222
Date: July 1, 2008

From: Daniel A. Shames MD FACS
Deputy Director, Office of Drug Evaluation III
CDER/FDA

To: File (DFS)

Applicant: Axcan Scandipharm, Inc.

Proposed Trade Name: Ultrase® MT capsules

PDUFA goal date: July 1, 2008

Formulation: Ultrase capsules come in three strengths, Ultrase MT12, MT18, and MT20, containing 13,800, 20,700 and 23,000 USP units (U) lipase, respectively.

Proposed indication: Treatment of exocrine pancreatic insufficiency (EPI)

Proposed regimen: 500 to 1,000 lipase USP units/kg/meal, not to exceed 2,500 USP units/kg/meal or 4,000 lipase USP units/g fat/day

Recommended Regulatory Action: Approvable (AE) because of CMC and Virology deficiencies.
Attribution: I primarily consulted the reviews of the Cross Discipline Team Leader, Ann Pariser MD and the Medical Reviewer, Jo Anna Ku MD for the creation of this Memorandum.

1.0 Background (General)

1.1 Pancreatic Enzymes

1.11 Clinical

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due a number of underlying diseases and conditions. Cystic Fibrosis (CF) is the most common cause of EPI in children, and chronic pancreatitis (CP) due to alcoholism or idiopathic pancreatitis is the most common cause of EPI in adults; however, there are a large number of other causes, such as pancreatectomy. Clinical manifestations of EPI are predominantly steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The main stay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause, has been the administration of pancreatic enzyme replacement therapy (PERT) with exogenous sources of pancreatic enzyme product (PEP).

1.12 Product

The drug substance (DS) is derived from porcine pancreas glands harvested from pigs raised as human food. The glands are obtained from slaughter houses, (b) (4) until they are processed by the manufacturer. The glands then undergo (b) (4) resulting in the pancrelipase DS to be used for manufacture of drug product (DP). Characterization of the enzymes contained in the DS, including assays for amylase, lipase, protease (total and a number of individual proteases, such as (b) (4)), and (b) (4) are performed.

1.13 Regulatory

PEPs are currently widely available in the United States (US) as non-prescription nutritional supplements or over-the-counter (OTC) medications, or by prescription. PEPs are available as enteric-coated/delayed-release and non-enteric coated formulations. These formulations are not considered to be interchangeable.

PEPs have been available in the US since prior to the Federal Food, Drug, and Cosmetic Act (The Act) of 1938. Most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962), and have never undergone formal evaluation under Investigational New Drug (IND) applications or NDAs for efficacy or safety. Substantial variations among currently marketed products exist, including variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (from lot to lot and even within lots). Variations in drug potency that result from this product variability are known to exist, and may significantly affect the safety and effectiveness of the PEPs.

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR):

- In 1979, the Agency proposed establishing monographs for OTC PEPs.
- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, preclearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.
- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.
- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.
- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an application as stated in 21CFR 314.50. A draft Guidance for submitting NDAs for PEPs was also published at that time.[1]

[1] 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." 2004.

- In 2006, the Final Guidance for submitting NDAs for PEPs was published (heretofore referred to as "the Guidance").[2]

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

Currently, there is only one approved NDA for a PEP: Cotazyme, an immediate-release PEP (NDA 20-580); however, Cotazym is not currently marketed in the US. Thus, no approved PEPs are currently commercially available in the US under NDA

2.0 NDA 22-222 (Ultrase)

2.1 Regulatory

This submission is the initial New Drug Application (NDA) for Ultrase MT (Ultrase). The Applicant is Axcan Scandipharm, Inc. This NDA was received as a rolling application. The first four Modules (Modules 1 through 4) were received on 01-July-2007. The fifth and final Module (Module 5) was received on 01-October-2007; receipt of this module started the review clock. The application was classified as a Priority review, and the PDUFA goal date was set as 01-April-2008. A major amendment, which included CMC information, was received on 12-March-2008. After receipt of the major amendment, the PDUFA goal date for the NDA was extended by three months by the Division, and the new PDUFA goal date was set as 01-July-2008.

2.2 Clinical

Ultrase and Ultrase MT, generally with formulations different from the to-be-marketed product (TbMP), have been extensively used clinically as commercially available products in many countries throughout the world, and Ultrase's long-term efficacy and safety is assumed. Per the Guidance, only short-term safety and efficacy studies were performed in support of this NDA.

The NDA submission contains efficacy and safety information from one short-term clinical safety and efficacy study (UMT20CF05-01; CF-01; Pivotal Study) in which the Ultrase TbMP was administered to pediatric and adult patients with CF, two supportive short-term clinical safety and efficacy studies (96-01 and 96-02) in which an older formulation of Ultrase (Eudragit formulation) was administered to pediatric and adult patients with CF, and one clinical bioavailability (BA) study (UMT20CP05-01; CP-01; BA Study) in adult patients with chronic pancreatitis (CP). Two additional open-label clinical studies, Study 01 and Study 02, were also submitted; however, these studies were not amenable to substantive review, and were considered only for supportive safety information by the Medical Reviewer. The most important clinical study for demonstrating efficacy was the Pivotal Study (CF-01).

2.21 Efficacy Analyses and Conclusions

2.211 UMT20CF05-01; CF-01

Study UMT20CF05-01 (Pivotal Study; Study CF-01) was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of Ultrase TbMP

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

administered to 31 patients with CF and EPI, ages 8 to 37 years. The objectives of the study were to describe the short-term (approximately 40 to 50 days of Ultrase TbMP treatment) efficacy and safety of Ultrase TbMP. Efficacy was assessed by the difference in a 72-hour fecal fat collection (CFA) during Ultrase TbMP treatment as compared to placebo treatment.

The primary efficacy endpoint was the comparison of percent coefficient of fat absorption (%CFA). %CFA is determined from a 72-hour stool collection (usually while the patient is consuming a high-fat diet) and is calculated as follows:

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

A change in %CFA of 30% or greater in severely affected patients (patients with a no-treatment %CFA of 40% or less) is considered to be clinically meaningful, but no accepted change in %CFA has been established for patients with no-treatment %CFA greater than 40%. However, change in %CFA with active treatment is expected to be larger in more severely affected patients, as the more severely affected patients have a greater capacity to respond to treatment. Thus, the results of the studies are expected to be at least partly dependent on the severity of patients disease (by no-treatment %CFA at Baseline) enrolled in the studies.

The primary efficacy endpoint results showed that mean CFA for patients during placebo treatment was 56%, and during Ultrase TbMP treatment was 89%. The difference in mean CFA on Ultrase TbMP as compared to placebo was 34%, which was a clinically meaningful and statistically significant difference ($p<0.0001$). There were no sequence or period effects seen for these results.

A subgroup/sensitivity analysis was performed by the Clinical Reviewer for change in CFA by placebo-treatment (no-treatment) CFA, where patients were evaluated by the no-treatment CFA subgroups of 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- and 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 showed that for the severely-affected patients (n=6), the mean CFA during placebo treatment was 24%, mean CFA during Ultrase TbMP treatment was 89%, and the mean difference on Ultrase 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 Ultrase treatment was 87%, and the mean difference on Ultrase 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 Ultrase treatment was 92%, and the mean difference on Ultrase as compared to placebo was 3%. This

difference is not 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 Ultrase treatment correlated strongly with no treatment-CFA. That is, patients with lower CFA while on no treatment had the greatest increases in CFA on Ultrase treatment and those with higher no-treatment CFA had smaller changes. These results are consistent with a clinically meaningful treatment benefit with Ultrase treatment in patients with moderate to severe no-treatment CFA.

Overall, the results for the primary endpoint demonstrate that treatment effect tends to have a linear relationship with the no-treatment condition of the patient. That is, patients who were more severely affected (lower no-treatment CFA) tended to have higher increases in CFA on Ultrase treatment. This result is consistent with a clinically meaningful treatment benefit with Ultrase in patients with moderate to severe no-treatment CFA. This result is also consistent with the previous experience with the PEPs as described in the medical literature, since patients with a lower CFA on no-treatment have a higher capacity to respond to treatment. No other factors were identified in this study that appeared to have an effect on response, including treatment sequence, age, or gender. Limitations in this study include the small numbers of patients included in the study, and the small number of patients in the severely-affected (n=6) subgroup.

Despite the limitations of the study, the results demonstrate a statistically significant and clinically meaningful benefit to treatment with Ultrase TbMP in patients with EPI due to CF, ages 8 to 37 years, and support the approval of Ultrase TbMP for the treatment of steatorrhea due to EPI.

2.212 Supportive Studies 96-01 and 96-02

The two supportive studies 96-01 and 96-02 were nearly identical in design, both being multi-center, randomized (1:1 to treatment sequence), DB, placebo-controlled, two-treatment, cross-over studies of Ultrase-Eudragit administration, and the design was similar to the design used in the Pivotal Study (CF-01). Both studies were completed more than ten years ago and used a different formulation of Ultrase than the Ultrase TbMP, with the formulations differing predominantly by the delayed-release coating of the Drug Product. Since comparability between the two formulations has not been demonstrated (in the BA study), the results of studies 96-01 and 96-02 cannot be used to provide primary evidence of efficacy (and safety) of Ultrase TbMP, and thus, will be used only as supportive evidence of efficacy (and safety).

The objectives of the studies were to describe the short-term efficacy and safety of Ultrase-Eudragit administered to a total of 57 patients with CF and EPI, ages 7 to 36 years. The primary efficacy endpoint was the difference in a 72-hour fecal fat collection (CFA) during Ultrase-Eudragit treatment as compared to placebo treatment. The two studies differed in that a higher-strength Ultrase-Eudragit capsule (Ultrase MT20) was administered in Study 96-01, and lower-strength Ultrase-Eudragit capsule (Ultrase MT12) was administered in Study 96-02.

The results for Study 96-01indicated that for the primary efficacy endpoint, the mean CFA on placebo treatment (n=25) was 59%, and the mean CFA on Ultrase-Eudragit

treatment (n=27) was 88%. The mean difference between the treatment periods was 29%, which was highly statistically significant (p=0.0001).

The results for the Study 96-02 indicated that for the primary efficacy endpoint the mean CFA on placebo treatment (n=22) was 47%, and the mean CFA on Ultrase-Eudragit treatment (n=23) was 79%. The mean difference between the treatment periods was 33%, which was highly statistically significant (p=0.0002).

2.213 Overall Efficacy Conclusion

These efficacy findings support the approval and labeling of Ultrase TbMP for the treatment of steatorrhea due to EPI from CF or other causes, in pediatric and adult patients, ages seven years and older.

2.22 Safety Analysis and Conclusion

In consideration of the long and extensive safety experience with the PEPs, the Guidance stated that it is not necessary to conduct long-term safety evaluations of the PEPs in support of the PEP NDAs; however, short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the Gastrointestinal (GI) tract and are not absorbed, the Guidance further recommended that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms (i.e., AEs) during these clinical trials.

One exception to the relative safety of the PEPs is the association of fibrosing colonopathy with PEP use. Fibrosing colonopathy associated with PEP use is rare, and although the etiology has not been completely elucidated, it has been assumed to be related to high or inappropriate dosing of PEPs. Thus, the Cystic Fibrosis Foundation in conjunction with the FDA have recommended that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal (FitzSimmons et al., 1997[3]; Borowitz et al., 2002[4]). Since publication of these recommendations, cases of fibrosing colonopathy have been reported only sporadically, and are unlikely to be reported during the relatively small clinical trials conducted in support of the PEP NDAs. Thus, continued monitoring for fibrosing colonopathy associated with PEP use is likely to best be performed through global safety surveillance.

Consistent with the Guidance, the safety evaluations performed for the Ultrase clinical development program focused predominantly on the monitoring of clinical signs and symptoms (i.e., AE assessments) during the short-term clinical efficacy and safety studies conducted with Ultrase, and no long-term safety studies were performed.

The safety information submitted in this NDA submission includes an Integrated Summary of Safety (ISS) and safety information from three individual clinical studies conducted with Ultrase (CF-01, 96-01 and 96-02). Thus, the submitted safety information consists of safety assessments obtained with both the Ultrase TbMP and

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[3] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with Cystic Fibrosis. N Engl J Med 1997;336:1283-1289.

[4] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with Cystic Fibrosis. J Pediatr Gastroenterol and Nutr 2002;35(3):246-259.

Eudragit formulations. The most important safety information available for review in the NDA submission was the safety data obtained from the Pivotal Study CF-01, which was performed with Ultrase TbMP. The Medical Reviewer analyzed the safety information from the Pivotal Study separately, and also pooled the electronic safety datasets for the three studies (CF-01, 96-01 and 96-02) so as to perform an independent review of the safety data contained in this NDA submission. The 120-Safety Update was also submitted during the review cycle (dated 01-February-2008), and the results were integrated by the Medical Reviewer in the overall safety analysis.

The Review Team concluded that this NDA submission provides evidence of short-term safety for Ultrase

2.3 Microbiology Analysis and Conclusion

The Microbiology Reviewer recommended an Approval action based on a satisfactory product quality microbiology review of the information submitted.

The Reviewer noted that the drug product consisted of solid non-sterile capsules with a core of minitablets composed of pancrelipase and compendial excipients. The drug product has a microbial limits release specification of no more than 10^3 CFU/g of total bacteria, no more than 10^2 CFU/g of total combined yeasts and molds, and an absence of *Salmonella* and *Escherichia coli* species. Overall, the specifications, analytical procedures, and stability were found to be acceptable, and no microbiology deficiencies were identified in the review.

2.4 Virology Analysis and Conclusion

The active pharmaceutical ingredient in Ultrase, pancrelipase, is derived from pig pancreas tissue. One batch of pancrelipase DS requires glands from (b) (4) pigs, and such a large quantity of raw material has to be obtained from by-products of slaughtered pigs. At the slaughterhouses, pigs introduced for slaughter are declared as fit for human consumption after they have been found to be healthy by visual inspection only. 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 primary Virology Review.

The overall assessment of the Virology Reviewer is there are a number of deficiencies in the DS manufacturer's viral risk mitigation plan. These deficiencies will be communicated to the DS manufacturer ((b) (4) in a letter dated July 1, 2008 (see Appendix 1 comments 20-23). The CMC DS deficiencies were sent in a letter by DTP to (b) (4) on April 16, 2008 (see Appendix 1, comments 1-19).

2.5 Non Clinical Pharmacology and Toxicology Analysis and Conclusion

PEPs have been widely used in clinical practice as treatments for EPI since prior to 1938, and there is a large amount of clinical experience with these products in human patients. Per the Guidance, 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 Ultrase clinical development program. However, toxicology studies are needed if the excipients in the Ultrase DP are not classified as GRAS. Consistent with

the Guidance, no new pharmacology or toxicology studies were conducted with Ultrase and no new non-clinical studies were submitted in the NDA submission.

The non-clinical information provided by the Applicant in the submission was mostly related to the excipients and phthalic acid, a major impurity in Ultrase capsules. Toxicology information on the excipients croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP-55), triethyl citrate, talc, and iron oxide was submitted in the application and in the IND for Ultrase (IND #41,387). The information was in the form of a summary report, along with reprints of the cited references. The information was limited to these excipients, since 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 Ultrase, and from information from the FDA Inactive Ingredients Database. The maximum daily dose level was estimated using the excipient levels from the DMF (for Drug Product), and an assumed maximum daily dose of 21,000 lipase U/kg/day and a body weight of 60 kg. Most of this information was previously reviewed in the Pharmacology Review of IND 41,837, dated 09-March-2007. New information provided in the NDA submission was also reviewed by the Toxicology Reviewer during the review cycle.

Overall, the assessment of the Reviewer was that the 105-week carcinogenicity study of phthalic anhydride in rats and other nonclinical studies of phthalic acid and phthalic anhydride provide a reasonable assurance of safety for the ingestion of phthalic acid associated with Ultrase administration.

2.6 Clinical Pharmacology Analysis and Conclusion

Clinical pharmacology information in this NDA submission consists of two studies. They are a bioavailability (BA) study UMT20CP05-01 (CP-01) and an *in vitro* stability study (RE-071211-01; Stability Study) of Ultrase TbMP sprinkled on food.

2.61 Bioactivity Study

The bioavailability (BA) study was a single-center, randomized, open-label, 2 X 2 cross-over, intubation study that evaluated the intra-duodenal delivery of lipase from two enteric-coated capsule formulations of Ultrase: the older formulation of Ultrase coated with Eudragit (Ultrase-Eudragit), which is not intended for marketing, and Ultrase coated with HP-55 (Ultrase TbMP), which is the intended to-be-marketed product. Twenty (20) adult chronic pancreatitis patients with EPI (CPPI; n=10) and without EPI (CP; n=10) were enrolled in the study.

The 90% CIs for the ratio of Ultrase-Eudragit vs. Ultrase TbMP in CPPI patients, CP patients, and for all patients combined was assessed, and none of the comparisons demonstrated comparable recovery from duodenal aspirations.

The conclusion of the Primary Reviewer was that that comparability of the two Ultrase formulations was not demonstrated.

2.62 Stability Study

The results of the *in vitro* study demonstrated that 60 minutes after being sprinkled on soft foods (i.e., applesauce, pudding, and yogurt), the Ultrase 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 Ultrase TbMP after opening the capsules and mixing the contents (minitablets) in soft acidic foods when intact capsules cannot be swallowed.

2.7 Chemistry Manufacturing and Controls Analyses and Conclusion

The Product Reviewer performed separate reviews of the Drug Substance (DMF # (b) (4) review), Drug Product (DMF #15681 review), and Packaging and Final Drug Product Release (Applicant, Axcan). The overall assessment of the CMC data submitted in the NDA amendment was that the application is Approvable with deficiencies noted for Drug Substance (DS), Drug Product (DP), and Packaging and Final Drug Product Release.

2.71 Drug Substance (DS)

The DS is manufactured by the (b) (4) ((b) (4) (b) (4) and (b) (4) is the Drug Master File (DMF) holder (DMF # (b) (4) The DMF was most recently updated 29-September-2007. The DMF was previously reviewed (# 5, 06-July-2004), and was determined to be inadequate due to deficiencies such as lack of DS characterization, inadequate manufacturing consistency, lack of in-process testing, lack of purity and identity testing, incomplete DS specifications, enzyme assay methods and validation, and a lack of sufficient stability data. Responses to the deficiencies identified in Review #5 were included in CMC DS review of the present Product Reviewer and were communicated to (b) (4) in a letter dated April 16, 2008 (Appendix I, comments 1-19). The DMF has been cross referenced by Axcan in NDA 22-222. A manufacturing facility inspection was not performed by the Agency during this review cycle.

2.72 Drug Product (DP)

The DP Ultrase is manufactured by Eurand S.p.A. (Eurand; Milano, Italy) from the (b) (4)-produced pancrelipase DS, and Eurand is the DMF holder (DMF #15681). The DMF was most recently updated 25-September-2007. The review of the DMF by the Product Reviewer is the first review of this DMF. The DMF has been cross referenced by Axcan in NDA 22-222. A manufacturing facility inspection was not performed by the Agency during this review cycle.

Ultrase capsules come in three strengths, Ultrase MT12, MT18, and MT20, containing 13,800, 20,700 and 23,000 USP units (U) lipase, respectively. There is no overage, and this product is labeled 100% of the label claim of lipase activity. Capsules contain enteric-coated minitablets of pancrelipase formulated with compendial excipients. All inactive ingredients used in the DP are USP/NF materials. These deficiencies will be communicated to the DP manufacturer (Eurand) in a letter dated July 1, 2008 (appendix 2 comments 1-9)

2.73 Packaging and Final Drug Product Release

Axcan Scandipharm (Axcan; Quebec, Canada) is responsible for packaging and final DP release. Final DP release testing includes assessment of release specifications, such as lipase, amylase, and protease activities, free phthalic acid, uniformity of dosage, and microbial limits testing, among others. Container/closure system (packaging) and shelf-life assessments are also assessed (shelf-life specifications are different from product

release specifications). A number of deficiencies in the packaging and final product release were noted by the Product Reviewer.

These deficiencies will be communicated to the Applicant in the Approvable letter (see Appendix III). In addition, the Applicant will be notified that there are deficiencies in the DS and DP DMFs supporting the application, although the specific deficiencies will not be communicated (trade secret information to be communicated directly to the DMF holders).

3.0 Regulatory Conclusion and Action

I agree with the conclusions and recommendations of the Review Team and CDTL that this Application (NDA 22-222) is Approvable based on CMC and Virology deficiencies. I will communicate these deficiencies in a regulatory letter to the Sponsor.

APPENDIX 1
Drug Substance (DMF (b) (4) (b) (4) Comments
CMC Comments 1-19 (sent 4/16/2008), Viral Comments 20-23 sent 1/7/2008

1. The amount of raw materials used in manufacturing DS should be clearly defined. Limits should be placed on all process-related impurities in DS or alternatively, their removal by the process must be validated.

2. 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. 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 through 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 DS can only be released upon FDA approval or using a protocol previously approved by the FDA.

5. 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. Provide results of a (b) (4) characterization study using olive oil as substrate.

7. Provide a DS characterization report for amylase.

8. 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 DS 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 DS) 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 DS. 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 DS. Provide information on the routine qualification of the lots of olive oil to ensure the consistency of the assay results.

13. Provide data that demonstrate that the enzymatic assay methods are performed such that the reaction product generated is linear with respect to time.

14. Provide data that demonstrate that other components in DS do not interfere with your enzymatic potency assays. This can be confirmed by (b) (4) into the DS.

15. Provide data to support that the assays validated for drug product release and stability are suitable to assay DS.

16. Provide additional stability data for 1208 and 1286 DS made in 2006 and 2007, and the trend of all stability data to give the 95% confidence interval about the trending line.

17. Identify an expiry or hold time for 1208 DS before (b) (4) and provide the data supporting your proposal.

18. Establish an expiry for (b) (4) API (1286 DS) based on relevant stability data, and provide the data supporting your proposal.

19. Provide your DS release test sampling plans.

20. 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. Comment on the risk to product quality due to the potential infection of swineherds with parasites.

c. Provide a detailed description of the sanitizing/cleaning procedures in place to prevent cross contamination between different batches of drug substance.

d. Provide a detailed description of your plan on how to prevent cross contamination with other 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 four years. The summary should include:
   i. Names and dates of all pancreatic tissue vendor audits.
   ii. Quality systems evaluated.
   iii. A representative Health Certificate for animal by-products from each of the approved vendors.

21. 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 samples 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) ((b) (4) (b) (4) step and the (b) (4) step share the same components potentially responsible for viral inactivation (i.e., (b) (4) and (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. 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. Provide a detailed description of the viral infectivity test procedures used for the evaluation of the (b) (4) (b) (4) (b) (4), and (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 brief 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.

22. Regarding the in-process viral infectivity tests, 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.

23. Regarding your viral control strategy:

a. Provide Q-PCR test results for all viruses that have been identified as having the potential to infect patients; this includes HEV, EMCV, SVDV, Reo, Rota A, influenza A, and VSV.

b. 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 for 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 II
Drug Product (DMF 15681/ Eurand) Comments 1-9

1. In regards to DP release specification and acceptance criteria, we have the following comments:

    a. Provide acceptance criteria for the identification assay (b) (4) assay).
    b. Include testing for (b) (4) content, product-related substances and impurities (i.e. degradants) to your release program.
    c. Provide an acceptance criterion with a range for capsule weight in your release program.
    d. Provide the release test sampling plans.

2. In regards to your DP stability program, we have the following recommendations:

    a. Include testing for (b) (4) content, product-related substances and impurities (i.e. degradants) in your stability program.
    b. Provide stability data with trend analysis on lots manufactured in 2006 and 2007.

3. We recommend that an internal reference standard that reflects the DP 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 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.

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. Provide the (b) (4) Assay method used in the (b) (4) step of manufacturing.

7. Describe the (b) (4) process used in the (b) (4) step of manufacturing, including in-process controls and related acceptance criteria.

8. Provide detailed information regarding the chemistry, manufacturing and controls for the hypromellose phthalate used for enteric coating of the minitablets.

9. Provide a summary of the process validation program. Process validation should be preformed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.

APPENDIX III (Sponsor Comments/Axcan Scandipharm)

1. We found that the DMFs supporting your application (DMF (b) (4) DMF 15681) are deficient. Letters stating all deficiencies will be 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.

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/s/

Daniel A. Shames
7/1/2008 12:46:18 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Summary Review of NDA 22-222
Ultrase MT (pancrelipase delayed-release capsules) for Exocrine Pancreatic Insufficiency

Date: July 1, 2008

From: Anne R. Pariser, M.D., Clinical Team Leader
Division of Gastroenterology Products (DGP)

To: Daniel A. Shames, M.D., Deputy Director
Office of Drug Evaluation III (ODE III)

Identifying Information

NDA #:	22-222
Applicant:	Axcan Scandipharm, Inc.
Product name:	Ultrase MT (pancrelipase delayed-release capsules)
Proposed Trade Names:	Ultrase MT
Submission date:	September 28, 2007
Stamp date:	October 1, 2007
PDUFA goal date:	July 1, 2008
Formulation:	Pancrelipase delayed-release capsules for oral administration
Proposed indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Proposed regimen:	Up to 2,500 lipase units per kg per meal, not to exceed 10,000 lipase units per kg per day

Recommended Regulatory Action: Approvable (AE) under 21 CFR 314.

I. Introduction, Background, and Regulatory History

A. Introduction

This submission is the initial New Drug Application (NDA) submission for Ultrase MT (Ultrase). The Applicant is Axcan Scandipharm, Inc. Ultrase is a New Molecular Entity (NME) that was granted priority review. This NDA submission was received on 01-October-2007, there was a major amendment received 12-March-2008, and the Prescription Drug User Fee Act (PDUFA) goal date is 01-July-2008.

B. Clinical Background

Ultrase (pancrelipase delayed-release capsules) is an enteric-coated, delayed-release pancreatic enzyme product (PEP). Ultrase is an exogenous source of porcine-derived pancreatic enzymes intended to treat steatorrhea due to exocrine pancreatic insufficiency (EPI). EPI typically results from chronic loss of pancreatic tissue due a number of underlying diseases and conditions. Cystic Fibrosis (CF) is the most common cause of EPI in children, and chronic pancreatitis (CP) due to alcoholism or idiopathic pancreatitis is the most common cause of EPI in adults; however, there are a large number of other causes,

such as pancreatectomy. Clinical manifestations of EPI are predominantly steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The main stay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause, has been the administration of pancreatic enzyme replacement therapy (PERT) with exogenous sources of PEPs.

C. Regulatory History of Pancreatic Enzyme Products

PEPs are currently widely available in the United States (US) as non-prescription nutritional supplements or over-the-counter (OTC) medications, or by prescription. PEPs are available as enteric-coated/delayed-release and non-enteric coated formulations. These formulations are not considered to be interchangeable.

PEPs have been available in the US since prior to the Federal Food, Drug, and Cosmetic Act (The Act) of 1938. Most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962), and have never undergone formal evaluation under Investigational New Drug (IND) applications or NDAs for efficacy or safety. Substantial variations among currently marketed products exist, including variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (from lot to lot and even within lots). Variations in drug potency that result from this product variability are known to exist, and may significantly affect the safety and effectiveness of the PEPs.

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR):

- In 1979, the Agency proposed establishing monographs for OTC PEPs.

- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, preclearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.

- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.

- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.

- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an

application as stated in 21CFR 314.50. A draft guidance for submitting NDAs for PEPs was also published at that time.[1]

- In 2006, the Final Guidance for submitting NDAs for PEPs was published (heretofore referred to as "the Guidance").[2]

- On October, 2008, Notice of Extension of the deadline was published, which stated that FDA would use enforcement discretion for the PEPs. Manufacturers must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010 in order to continue marketing their products.

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

Currently, there is only one approved NDA for a PEP, Cotazyme, an immediate-release PEP (NDA 20-580); however, Cotazym is not currently marketed in the US. Thus, no approved PEPs are currently commercially available in the US under NDA.

D. Regulatory History of Ultrase

The regulatory history for Ultrase is summarized as follows:

- Ultrase has been commercially available in the US since 1991. Axcan began marketing Ultrase in the US in August 1999. Prior to this date, Ultrase was marketed by Scandipharm, Inc.

- The original IND submission (#41,387) for Ultrase was received by the Agency on 24-December-1992.

- An NDA for Ultrase was submitted in 1994 (NDA #20-480); however, this NDA does not appear to have been filed. The original correspondence from 1994 is unavailable and the reasons for not filing are not clear; however, it appears that the studies contained in the application were not adequate to support an NDA approval for Ultrase. At that time, the Division recommended that the Applicant conduct adequate and well-controlled fat absorption studies with Ultrase administration to CF patients that would support a future NDA.

- Several meetings between the Applicant and the Division have occurred between 2003 and 2007 (prior to submission of this NDA). Relevant discussions and agreements that occurred at these meetings include the following:

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[1] 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." 2004.

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

- The Division informed Axcan that equivalence (comparability) of a previous formulation of Ultrase with Eudragit coating (Ultrase-Eudragit) and the newer formulation of Ultrase with an HP-55 coating that is the intended to-be-marketed product (Ultrase TbMP) could not be established solely by chemistry, manufacturing, and controls (CMC) means (e.g., dissolution testing), and comparability testing must include clinical assessments in addition to CMC assessments (e.g., *in vivo* bioactivity testing or clinical outcome measures).

- Extensive discussions regarding CMC for Drug Substance (DS), Drug Product (DP), and viral risk assessment and mitigation strategies have taken place. The Agency provided a large amount of advice regarding such things as characterization, assay validation, stability testing, and viral risk assessment, among others, to the Applicant and to the Drug Master File (DMF) holders for the DS ((b) (4) and the DP (Eurand S.p.A.) (please see the Meeting Minutes for these meetings for the complete responses and advice given to the Applicant and DMF holders).

- The Division stated that an age-appropriate formulation for younger pediatric patients would need to be developed, and the dose strengths of this formulation should provide for sufficient flexibility to allow for recommended weight-based dosing in younger patients. It was additionally noted that proposed studies in pediatric patients, ages two to 11 years, would likely support labeling of the product for patients two years of age and older only, and the Applicant would need to address all pediatric subgroups (i.e., patients less than two years of age) in order to meet PREA requirements. Axcan stated their intention to request a pediatric deferral (to study patients less than two years of age) around the time of NDA submission to allow for time to develop a pediatric formulation for younger patients.

- Ultrase received Fast Track designation on 30-May-2007.

- This NDA was received as a rolling application. The first four Modules (Modules 1 through 4) were received on 31-July-2007. The fifth and final Module (Module 5) was received on 01-October-2007; receipt of this module started the review clock. The application was classified as a Priority review, and the PDUFA goal date was set as 01-April-2008. A major amendment, which included CMC information, was received on 12-March-2008. After receipt of the major amendment, the PDUFA goal date for the NDA was extended by three months by the Division, and the new PDUFA goal date was set as 01-July-2008.

- At the time of NDA submission, the Applicant submitted a pediatric deferral request, requesting that the evaluation of Ultrase in children less than two years of age be deferred until the post-marketing period, to allow additional development time for an infant-specific formulation.

- At least four Information Request (IR) letters were sent to the Applicant during the review cycle, including requests for information on CMC/product quality, Clinical Pharmacology, the proposed trade name, labeling, and the proposed pediatric deferral request (IR letters dated 06-December-2007, 15-January-2008, 05-February-2008, and 24-June-2008).

- A mid-review informational meeting was held between the Division and the Applicant on 16-January-2008, where deficiencies that were important to assessing the approvability of Ultrase that had been identified at that point in the review cycle were communicated to the Applicant (see Meeting Minutes, dated 26-January-2008). Issues related to Drug Substance, Drug Product, Clinical Pharmacology, Clinical, and the proposed trade name were discussed at this meeting.

The primary review disciplines have all written review documents for this NDA, which should be consulted for more specific details. This memorandum summarizes selected information from these documents. The primary review documents relied upon include the following:

- Clinical Review: Joanna W. Ku, M.D., dated 01-July-2008.
- Statistical Review and Evaluation, Clinical Studies: Stella Grosser, Ph.D., dated 25-June-2008.
- Pharmacology/Toxicology Review: David B. Joseph, Ph.D., dated 04-March-2008.
- Clinical Pharmacology Review: Tien-Mien Chen, Ph.D., dated 10-March-2008.
- CMC Drug Product Review (review of Drug Master File [DMF] #15681): Wei Guo, Ph.D., dated June, 2008.
- CMC Drug Substance Review (review of DMF # (b) (4) Wei Guo, Ph.D., dated June, 2008.
- CMC Review of Packaging and Final Drug Product Release (for Applicant Axcan): Wei Guo, Ph.D., dated June, 2008.
- Product Quality Microbiology Review: Stephen E. Langille, Ph.D., dated 29-January-2008.
- Virology Review: Ennan Guan, Ph.D., dated June, 2008.
- Clinical Inspection Summary Memorandum: Khairy W. Malek, M.D., dated 21-February-2008.
- Division of Medication Errors Prevention Proprietary Name Risk Assessment, and Label and Labeling Review: Denise Baugh, dated 03-June-2008.

Since an Approvable Action is recommended, no labeling or post-marketing commitments were negotiated during this review cycle, and no Advisory Committee was convened.

II. Chemistry, Manufacturing and Controls

CMC data have been extensively reviewed by the Product Reviewer (Wei Guo, Ph.D.), Microbiology Reviewer (Stephen Langille, Ph.D.), and Virology Reviewer (Ennan Guan, Ph.D.). Please refer to the Drug Substance (DMF # (b) (4) Drug Product (DMF #15681), Packaging and Final Drug Product Release (Applicant, Axcan), Microbiology, and Virology reviews for more detailed information. Important issues identified in the Product, Microbiology, and Virology reviews are summarized as follows:

A. Product Review

The Product Reviewer (Dr. Guo) performed three separate reviews of the Drug Substance (DMF # (b) (4) review), Drug Product (DMF #15681 review), and Packaging and Final Drug Product Release (Applicant, Axcan). The overall assessment of the CMC data submitted in the NDA amendment was that the application is Approvable with deficiencies noted for Drug Substance (DS), Drug Product (DP), and Packaging and Final Drug Product Release. Each review will be considered separately, as follows:

1. Drug Substance (DS)

The DS is manufactured by the (b) (4) ((b) (4) (b) (4) and (b) (4) is the Drug Master File (DMF) holder (DMF # (b) (4) The DMF was most recently updated 29-September-2007. The DMF was previously reviewed (DMF Review #5; by Haber, M., Ph.D., dated 06-July-2004), and was determined to be inadequate due to deficiencies such as lack of DS characterization, inadequate manufacturing consistency, lack of in-process testing, lack of purity and identity testing, incomplete DS specifications, enzyme assay methods and validation, and a lack of sufficient stability data. Responses to the deficiencies identified in Review #5 were included in this CMC DS review by Dr. Guo.

The DMF has been cross referenced by Axcan in NDA 22-222. A manufacturing facility inspection was not performed by the Agency during this review cycle.

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) The glands (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as mincing, (b) (4) (b) (4) and (b) (4) (among others), which results in pancrelipase DS. The resulting pancrelipase DS is used for manufacture of DP.

The overall findings of the Product Reviewer were that there were a large number of deficiencies identified for the DS manufacturing and controls. It is additionally noted that there are viral risk mitigation plan deficiencies with the DS that were noted by the Virology Reviewer (see Virology review in Section II.C. below), which are summarized separately. DS manufacturing and controls findings that were identified as approvability issues by Dr. Guo include deficiencies in:

- Definitions and limits for raw materials used in manufacturing.
- Acceptance criteria for lipase, amylase, and protease specific activities, (b) (4) content and microbial limits for (b) (4) (b) (4) and expiration dating and the data to support stability.
- Data to support the operating and performance parameters used in manufacturing, and the acceptance range of yield for each critical manufacturing step.
- In-process control testing acceptance criteria for lipase activity and microbial limits before and after enzyme activation.
- Characterization of (b) (4) using olive oil as substrate.
- Characterization for amylase.
- API DS release and stability testing specifications.
- Acceptance criteria for HPLC analysis method for the various peaks observed.
- Release and stability testing for (b) (4) content, and product-related substance and impurities, including degradants.
- Acceptance criteria for protease and amylase activity of (b) (4) API. Criteria were noted to be too wide to ensure consistent manufacture of drug product.
- Adequate control of (b) (4) quantity and activity for DS.
- Characterization for olive oil used in the lipase activity assay of DS.
- Data that demonstrate that the enzymatic assay methods are linear with respect to time.
- Data that demonstrate that other components in DS do not interfere with enzymatic potency assays.
- Data to support that the assay validated for drug product release and stability are suitable to assay DS.
- Stability data for DS made in 2006 and 2007.
- Data to identify an expiry or hold time for DS before (b) (4)
- Establishment of DS release test sampling plans.
- It was also noted that lots failing microbial specifications were reprocessed and released, which is not acceptable without FDA approval.

These deficiencies and the viral risk mitigation plan deficiencies, which also pertain to the DS, will be communicated to the DS manufacturer ((b) (4) in a letter that will be sent by the Division of Therapeutic Proteins (DTP). The letter will include the following comments on the deficiencies noted in the DS and Virology reviews (please see Dr. Guo's and Dr. Guan's reviews for a complete listing of the deficiencies, and the letter to (b) (4) for the final wording).

1. The amount of raw materials used in manufacturing DS should be clearly defined. Limits should be placed on all process-related impurities in DS or alternatively, their removal by the process must be validated.

2. 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. 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 through 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 DS can only be released upon FDA approval or using a protocol previously approved by the FDA.

5. 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. Provide results of a (b) (4) characterization study using olive oil as substrate.

7. Provide a DS characterization report for amylase.

8. 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 DS 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 DS) 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 DS. 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 DS. Provide information on the routine qualification of the lots of olive oil to ensure the consistency of the assay results.

13. Provide data that demonstrate that the enzymatic assay methods are performed such that the reaction product generated is linear with respect to time.

14. Provide data that demonstrate that other components in DS do not interfere with your enzymatic potency assays. This can be confirmed by (b) (4) into the DS.

15. Provide data to support that the assays validated for drug product release and stability are suitable to assay DS.

16. Provide additional stability data for 1208 and 1286 DS made in 2006 and 2007, and the trend of all stability data to give the 95% confidence interval about the trending line.

17. Identify an expiry or hold time for 1208 DS before (b) (4) and provide the data supporting your proposal.

18. Establish an expiry for (b) (4) API (1286 DS) based on relevant stability data, and provide the data supporting your proposal.

19. Provide your DS release test sampling plans.

20. 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. Comment on the risk to product quality due to the potential infection of swineherds with parasites.

    c. Provide a detailed description of the sanitizing/cleaning procedures in place to prevent cross contamination between different batches of drug substance.

    d. Provide a detailed description of your plan on how to prevent cross contamination with other 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 four years. The summary should include:
        i. Names and dates of all pancreatic tissue vendor audits.
        ii. Quality systems evaluated.

iii. A representative Health Certificate for animal by-products from each of the approved vendors.

21. 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 samples 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) ((b) (4) (b) (4) step and the (b) (4) step share the same components potentially responsible for viral inactivation (i.e., (b) (4) and (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. 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. Provide a detailed description of the viral infectivity test procedures used for the evaluation of the (b) (4) (b) (4) (b) (4) and (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 brief 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.

22. Regarding the in-process viral infectivity tests, 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.

23. Regarding your viral control strategy:

    a. Provide Q-PCR test results for all viruses that have been identified as having the potential to infect patients; this includes HEV, EMCV, SVDV, Reo, Rota A, influenza A, and VSV.

    b. 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 for those viruses that potentially can infect humans, and conducting infectivity testing of Q-PCR positive batches is appropriate.

    c. Although you plan to [redacted] (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 [redacted] (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.

2. Drug Product (DP)

The DP Ultrase is manufactured by Eurand S.p.A. (Eurand; Milano, Italy) from the [redacted] (b) (4)-produced pancrelipase DS, and Eurand is the DMF holder (DMF #15681). The DMF was most recently updated 25-September-2007. The review of the DMF by the Product Reviewer (Dr. Guo) is the first review of this DMF. The DMF has been cross referenced by Axcan in NDA 22-222. A manufacturing facility inspection was not performed by the Agency during this review cycle.

The DMF describes the manufacturing of DP, Eurand Minitabs pancrelipase product with hypromellose phthalate (HP-55) coating. The manufacturing process for DP is divided into [redacted] (b) (4) parts:

[redacted] (b) (4)

(b) (4)

[redacted]

Ultrase capsules come in three strengths, Ultrase MT12, MT18, and MT20, containing 13,800, 20,700 and 23,000 USP units (U) lipase, respectively. There is no overage, and this product is labeled 100% of the label claim of lipase activity. Capsules contain enteric-coated minitablets of pancrelipase formulated with compendial excipients. All inactive ingredients used in the DP are USP/NF materials. The composition and strengths of DP are summarized in the following table (electronically copied and reproduced from Dr. Guo's review):

Table 1: Ultrase Drug Product Composition and Capsule Strengths

Components	Function	Ultrase MT 12	Ultrase MT 18	Ultrase MT 20
Lipase Activity	**USP Units/cps**	13,800	20,700	23,000
Capsule Size		[redacted]		

(b) (4)

(b) (4)

[redacted]

The minitablets contained in the Ultrase capsules are enteric-coated with hydroxypropyl methylcellulose phthalate (HPMCP), also called hypromellose phthalate, which is a chemical often used as an enteric-coating material to make delayed-release drug products. The grade of the material used for enteric coating of the minitablets is HP-55, which means that the polymer is designed to dissolve at pH above 5.5.

Note: Phthalic acid is a breakdown product of the hypromellose phthalate coating material. During the review cycle, Health Canada notified FDA that monoethyl phthalate and its

glucuronide (a metabolite of diethyl phthalate) had been detected in the urine of CF patients, which is thought to be from the enteric coating of delayed-release PEPs. More information is required from the Applicant regarding the chemistry, manufacturing and controls for the hypromellose phthalate used for the enteric coating of the minitablets.

The overall findings of the Product Reviewer were that there were a number of deficiencies identified for the manufacture of DP, including deficiencies in:

- Release and acceptance criteria.
- Stability data.
- Internal reference standards that reflect the DP commercial manufacturing process.
- Development and implementation of an internal working lipase reference standard.
- Qualification for the lipase olive oil substrate
- (b) (4) Assay method used in the (b) (4) step of manufacturing.
- Description of the (b) (4) process for the (b) (4) step of manufacturing.
- Information regarding the CMC for hypromellose phthalate used for the enteric coating of the minitablets.
- Summary of the process validation program.

These deficiencies will be communicated to the DP manufacturer (Eurand) in a letter that will be sent by DTP. These deficiencies are summarized as follows (please see Dr. Guo's review for a complete listing of the deficiencies, and the letter to Eurand for the final wording):

1. In regards to DP release specification and acceptance criteria, we have the following comments:

    a. Provide acceptance criteria for the identification assay (b) (4) assay).
    b. Include testing for (b) (4) content, product-related substances and impurities (i.e. degradants) to your release program.
    c. Provide an acceptance criterion with a range for capsule weight in your release program.
    d. Provide the release test sampling plans.

2. In regards to your DP stability program, we have the following recommendations:

    a. Include testing for (b) (4) content, product-related substances and impurities (i.e. degradants) in your stability program.
    b. Provide stability data with trend analysis on lots manufactured in 2006 and 2007.

3. We recommend that an internal reference standard that reflects the DP 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 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.

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. Provide the (b) (4) Assay method used in the (b) (4) step of manufacturing.

7. Describe the (b) (4) process used in the (b) (4) step of manufacturing, including in-process controls and related acceptance criteria.

8. Provide detailed information regarding the chemistry, manufacturing and controls for the hypromellose phthalate used for enteric coating of the minitablets.

9. Provide a summary of the process validation program. Process validation should be preformed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.

3. Packaging and Final Drug Product Release

Axcan Scandipharm (Axcan; Quebec, Canada) is responsible for packaging and final DP release. The DS is manufactured by (b) (4) and the DP is manufactured by Eurand.

The packaging procedure includes (b) (4) steps, as follows:

(b) (4)

Final DP release testing is performed by Axcan. This includes assessment of release specifications, such as lipase, amylase, and protease activities, free phthalic acid, uniformity of dosage, and microbial limits testing, among others. Container/closure system (packaging) and shelf-life assessments are also assessed (shelf-life specifications are different from product release specifications). A number of deficiencies in the packaging and final product release were noted by Dr. Guo, including deficiencies in:

- Real-time stability data to support a 24-month expiry. Several Out of Specification (OOS) findings that do not support the proposed expiry dating were also noted.

- Stability data on DP lots manufactured in 2006 and 2007.
- Tests for (b) (4) content, product-related substances and impurities in DP release, and stability programs.
- Reliance on USP lipase reference standard. There was a lack of internal working reference standard for lipase.

These deficiencies will be communicated to the Applicant in the Approvable letter. In addition, the Applicant will be notified that there are deficiencies in the DS and DP DMFs supporting the application, although the specific deficiencies will not be communicated (trade secret information to be communicated directly to the DMF holders). These deficiencies are summarized as follows (please see Dr. Guo's review for a complete listing of the deficiencies, and the Approvable letter to Axcan for the final wording):

1. We found that the DMFs supporting your application (DMF (b) (4) DMF 15681) are deficient. Letters stating all deficiencies will be 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.

4. Product Review Summary

The overall assessment of the Product Reviewer (Dr. Guo) for the CMC data submitted in the NDA is that the application is Approvable (AE) with deficiencies noted for DS, DP,

and packaging and final DP release. The deficiencies for DS and DP are to be communicated in separate letters to the DS manufacturer ((b) (4) and to the DP manufacturer (Eurand), respectively, and the deficiencies for packaging and final DP release will be communicated directly to the Applicant in the Approval letter.

B. Microbiology Review

The Microbiology Reviewer (Dr. Langille) recommended an Approval action based on a satisfactory product quality microbiology review of the information submitted.

Dr. Langille noted that the drug product consisted of solid non-sterile capsules with a core of minitablets composed of pancrelipase and compendial excipients. The drug product has a microbial limits release specification of no more than 10^3 CFU/g of total bacteria, no more than 10^2 CFU/g of total combined yeasts and molds, and an absence of *Salmonella* and *Escherichia coli* species. Overall, the specifications, analytical procedures, and stability were found to be acceptable, and no microbiology deficiencies were identified in the review.

The Microbiology Reviewer did not recommend any comments relating to the microbiology information be communicated to the Applicant.

C. Virology Review

The Virology Reviewer (Dr. Guan) performed a detailed review of the virology information submitted in the NDA. Dr. Guan's findings are as follows:

The active pharmaceutical ingredient in Ultrase, pancrelipase, is derived from pig pancreas tissue. One batch of pancrelipase DS requires glands from (b) (4), and such a large quantity of raw material has to be obtained from by-products of slaughtered pigs. At the slaughterhouses, pigs introduced for slaughter are declared as fit for human consumption after they have been found to be healthy by verification of the government veterinarian. After harvesting, the glands are (b) (4), and prior to processing, the glands are (b) (4). 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 Dr. Guan's review.

The Agency has had numerous discussions with the DS manufacturer ((b) (4) prior to and during this NDA review cycle regarding procedures and plans for viral risk assessment and mitigation. In response to the Agency's previous requests, (b) (4) has agreed to provide information and will have procedures and plans for:

- Animal disease surveillance.
- Emerging viruses.
- Future development for viral inactivation or removal.
- Sanitation and cleaning procedures for equipment.

- Prevention of cross-contamination with materials from other species (e.g., ruminant tissue), including facilities dedicated to porcine species only.

However, (b) (4) did not provide their plans for any of these issues in this NDA submission.

Viral inactivation steps are involved in the DS manufacturing process, including (b) (4) (b) (4) with (b) (4) ((b) (4) and a (b) (4) step. Viral inactivation was evaluated by (b) (4) for the (b) (4) step only (after (b) (4) with (b) (4) at a (b) (4) which revealed two to three log inactivation of enveloped viruses and the non-enveloped virus Reo3, but not PPV. This result is consistent with results submitted by other DS manufacturers. (b) (4) did not evaluate viral inactivation for the (b) (4) step, nor after the (b) (4) step. The (b) (4) step is performed at (b) (4) but this step is not thought to have much effect on viral inactivation ((b) (4) notes that (b) (4)). Dr. Guan additionally notes that during the 16-January-2008 meeting held between the Division and the Applicant ((b) (4) was present at this meeting), (b) (4) was asked to perform an evaluation of additional steps for reduction of potentially pathogenic enveloped and non-enveloped viruses. In response to this request, (b) (4) has initiated an evaluation of the (b) (4) step, the (b) (4) step, and the (b) (4) (b) (4) step; however, Dr. Guan notes that (b) (4) manufacturing process at this point appears to possess less viral inactivation capacity than the processes for the two other PEPs recently reviewed.

Model viruses were selected for assessment of the viral clearance and validation of the manufacturing process. The selection of model viruses for viral clearance and validation generally should include relevant viruses that are known to or likely to contaminate the source material, are a broad range of virus types that display different physicochemical properties, and any selected model virus should be able to grow as a high titer stock and have ease of detection with a sensitive and reliable assay. The model viruses selected in the original NDA submission were assessed by Dr. Guan as not adequate, since there was no representative model for HEV and EMCF, but in response to an information request by the Division, (b) (4) added FCV and EMCF as models. The model viruses selected with the additional of FCV and EMCF were then assessed as covering all relevant viral characteristics and most of the relevant viruses, and the general plan was felt to be suitable for validation of the manufacturing process for viral clearance in accordance with ICH Q5A guidelines.

For the results of the viral inactivation/clearance studies reported in the submission, Dr. Guan notes the following:

- The only viral inactivation study reported involved the (b) (4) (b) (4) step ((b) (4) (b) (4) The results show the (b) (4) treatment inactivates the model enveloped viruses and Reo3, but not PPV. However, no information was submitted regarding the mechanism responsible for the inactivation. Dr. Guan noted that since this process step also includes pancreatic enzymes, the Applicant should demonstrate that the (b) (4) (b) (4) is responsible for the viral inactivation observed.

- In response to the Division's request for evaluation of additional viral inactivation steps, (b) (4) recently initiated (b) (4) step and (b) (4) step assessments for viral inactivation, and added EMCF and FCV for evaluation. These data are not yet available.

- (b) (4) did not provide information on the potential enveloped viral loads. Given the large amounts of PPV and PCV associated with this tissue source, the possibility exists that large viral titers of other viruses may also be present; therefore, it was not possible to provide a meaningful assessment of (b) (4) risk management strategy without this information. To resolve this issue, DTP requested that (b) (4) provide information on the potential enveloped viral loads in the starting material by implementing Q-PCR testing, and that the company model the capacity of the manufacturing process to inactivate enveloped viruses (e.g., using swine influenza A and VSV).

- (b) (4) has developed Q-PCR testing for non-enveloped, highly-resistant, pathogenic and non-pathogenic viruses, including PPV, SVDV, HEV, EMCV, PTV, Rota A, and PCV. (b) (4) stated that 50 batches have been tested and all batches tested negative for all of these viruses except PPV and PCV (Dr. Guan was only able to locate 20 batches in the submission). Dr. Guan notes that Q-PCR testing does not provide information on whether live viruses are present in the final product, and no infectivity testing results with PPV and PCV were provided. Thus, the manufacturing process and its associated controls do not demonstrate that the product is suitable for its intended purpose with respect to risk from viral contamination. (b) (4) will need to implement routine testing for non-enveloped viruses by Q-PCR, set limits for PPV in the final product, and demonstrate that their final product is free of infectious PCV 1 and 2.

The overall assessment of the Virology Reviewer is there are a number of deficiencies in the DS manufacturer's viral risk mitigation plan. Dr. Guan recommended that these deficiencies be communicated to the DS manufacturer ((b) (4) in a letter. The virology deficiencies, along with the CMC DS deficiencies, will be sent in a letter by DTP to (b) (4) (a listing of the deficiencies to be communicated is located in Section II.A.1., Drug Substance review, above).

III. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacotoxicology data have been reviewed in detail by the Animal Pharmacotoxicology Reviewer (David Joseph, Ph.D.); please refer to this review for more information.

PEPs have been widely used in clinical practice as treatments for EPI since prior to 1938, and there is a large amount of clinical experience with these products in human patients. Per the Guidance, 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 Ultrase clinical development program. However, toxicology studies are needed if the excipients in the Ultrase DP are not classified as GRAS. Consistent with the Guidance, no new pharmacology or toxicology studies were conducted with Ultrase and no new non-clinical studies were submitted in the NDA submission.

The non-clinical information provided by the Applicant in the submission was mostly related to the excipients and phthalic acid, a major impurity in Ultrase capsules. Toxicology information on the excipients croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP-55), triethyl citrate, talc, and iron oxide was submitted in the application and in the IND for Ultrase (IND #41,387). The information was in the form of a summary report, along with reprints of the cited references. The information was limited to these excipients, since 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 Ultrase, and from information from the FDA Inactive Ingredients Database. The maximum daily dose level was estimated using the excipient levels from the DMF (for Drug Product), and an assumed maximum daily dose of 21,000 lipase U/kg/day and a body weight of 60 kg. Most of this information was previously reviewed in the Pharmacology Review of IND 41,837, dated 09-March-2007. New information provided in the NDA submission was also reviewed by Dr. Joseph during the review cycle.

The toxicology findings in Dr. Joseph's review are notable for the following:

- Croscarmellose sodium is a cross-linked form of sodium carboxymethylcellulose. Croscarmellose is widely used in oral pharmaceutical formulations as a disintegrant. For patients treated with Ultrase, the maximum daily dose of croscarmellose sodium is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60 kg patient. An intake of Croscarmellose sodium 30 g/day has been recommended as the upper limit of safety for modified celluloses in general (National Research Council, 1989), which far exceeds the (b) (4) g/day exposure with Ultrase (in a 60 kg patient).

  Since Ultrase is intended for chronic use, the Applicant also submitted a published report that showed the no observed adverse effect level (NOAEL) for croscarmellose sodium in a 90-day oral (dietary) toxicity study in rats was 50,000 ppm, equivalent to 3,922 mg/kg/day in males and 4,712 mg/kg/day for females. Although six-month toxicity studies are usually needed to assess the safety of chronically administered medications (such as PEPs), some assurance of safety can be derived from this 90-day toxicity study since the NOAEL exceeded the estimated maximum human dose by 456-fold.

  Croscarmellose sodium also had no effects on embryo-fetal development in a teratogenicity study in which rats were orally administered of up to 50,000 ppm croscarmellose sodium (approximately 4,554 mg/kg/day).

- HP-55 is used in oral pharmaceutical formulations as an enteric-coating material. The maximum dose of HP-55 in patients treated with Ultrase is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60 kg patient. Chronic oral toxicity studies were submitted by the Applicant. In a six-month oral toxicity study in rats, HP-55 produced no adverse effects at doses of up to 6 g/kg/day. A 27-week oral (dietary) toxicity study in Beagle dogs was performed using dose levels of 0, 0.75, 1.5, and 3 g/kg/day HP-55. Soft stools and diarrhea were seen at the 1.5 and 3 mg/kg/day dose

levels during the first six weeks of treatment. Otherwise, HP-55 had no effects on most of the standard toxicology study parameters (histopathology results were not reported). Although a safety margin in dogs cannot be derived due to the absence of histopathology information, the dose levels used in this study exceeded the estimated maximum daily dose in humans by 17- to 68-fold. Thus, based on the chronic toxicity studies and previous human experience, the estimated maximum dose for HP-55 resulting from Ultrase administration is not considered to be a safety concern.

HP-55 also had no effects on embryo-fetal development in rats, other than delayed ossification at the highest dose tested (2,400 mg/kg/day). No embryo-fetal effects occurred in mice following oral administration of up to 4 g/kg/day on Days 7 to 12 of pregnancy.

- Triethyl citrate has been used in oral pharmaceutical formulations and as a direct food additive. Triethyl citrate is classified as GRAS for use as a direct food substance, with no limitation on its use other than current good manufacturing practice. The maximum daily dose of triethyl citrate in patients treated with Ultrase is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg in a 60 kg patient. The Joint FAO/WHO Expert Committee on Food Additives designated the acceptable daily intake (ADI) for triethyl citrate as 0 to 20 mg/kg in 1984 and again in 1999. The estimated maximum daily dose (4.4 mg/kg/day) falls within the ADI range. In a two-year oral (dietary) toxicity study in rats, triethyl citrate produced a dose-dependent decrease in weight gain and food intake at dose levels of 150, 1,000, and 1,500 mg/kg/day. No other adverse effects were seen. The Applicant also submitted a six-month oral chronic toxicity study in dogs where the NOAEL was 280 mg/kg/day, the highest dose tested. However, liver injury occurred in dogs at oral doses of 2,800 and 4,000 mg/kg/day given for seven to 12 weeks. Based on the chronic toxicity studies, previous human experience, regulatory information, and the recommended ADI, the estimated maximum dose of triethyl citrate resulting from Ultrase administration is not considered to be a safety concern.

- Talc is a finely powdered mineral composed of hydrated magnesium silicate. Talc is often used as a food additive or as an anti-caking agent, coating agent, or texturing agent in pharmaceutical products. Talc is classified as a color additive for drugs, and is listed in the Food Chemical Codex (Edition V) as a food additive. The maximum daily dose of talc in patients treated with Ultrase is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60 kg patient. The Joint FAO/WHO Expert Committee on Food Additives has designated the ADI as "not specified", a term that is applied to a food substance of very low toxicity. No oral toxicology studies of talc are available. However, results from animal studies suggest that the absorption of talc is limited. Based on the previous human experience, regulatory information, and the recommended ADI, the estimated maximum dose of talc resulting from Ultrase administration is not considered to be a safety concern.

  Talc also had no effects on embryo-fetal development with oral administration of talc in pregnant rats, mice, and hamsters.

- The Applicant submitted a summary report of toxicology information on o-phthalic acid (phthalic acid), a major impurity in Ultrase, and toxicology and pharmacokinetic (PK) information about phthalic anhydride (phthalic anhydride rapidly converts to phthalic acid in water and biological fluids). The presence of phthalic acid is due to degradation of the excipient hydroxypropyl methylcellulose phthalate, and the acceptance criterion for phthalic acid at release and during shelf life is not more than (b)(4)% w/w. The maximum dose of phthalic acid from Ultrase is estimated to be (b)(4) mg/kg/day. Since Ultrase is used as long-term therapy, chronic toxicity studies would be most relevant to the safety assessment of phthalic acid intake from Ultrase, although studies of 14 to 90 days are considered as acceptable for impurity qualification studies (ICH Guidance Q3B(R)). The summary report showed the following:

    - Phthalic anhydride was tolerated in rats at oral doses of up to 1,250 mg/kg/day given for seven weeks, but treatment with 2,500 mg/kg/day produced a 25% weight gain.

    - Phthalic acid tested negative in the Ames test, Rec +/- assay for DNA damage, chromosomal aberration assay, sister chromatid exchange assay, and HPRT mutation test. However, positive results were observed in *in vivo* assays in mice for the induction of dominant lethal mutations and sperm head abnormalities by phthalic acid. Phthalic anhydride was negative in the Ames test, SHE cell transformation assay, and the rat hepatocyte alkaline elution assay for DNA damage. In a 105-week carcinogenicity study in rats, phthalic anhydride produced no neoplastic or non-neoplastic lesions at oral doses up to approximately 750 mg/kg/day. A 104-week carcinogenicity study of phthalic anhydride was conducted in mice using oral dose levels of approximately 3,000/1,500 and 6,000/3,000 mg/kg/day in males and 3,000/750 and 6,000/1,500 mg/kg/day in females (the dose levels were reduced during the study due to excessive growth depression). Tumorigenic effects were not observed; however, an increased incidence of lymphocytosis in lungs and kidneys, and bile duct inflammation were observed in males and females at both dose levels.

    - Oral administration of up to 2,981 mg/kg/day phthalic acid in pregnant rats did not produce embryo-fetotoxicity or teratogenic effects; however, maternal toxicity (reduced weight gain and food consumption) was observed in the 1,763 and 2,981 mg/kg/day dose groups.

    - Phthalic acid did not produce adjuvant effects in the production of ovalbumin-reactive antibodies in mice following sensitization. No suppression of the antigenic response to ovalbumin was observed with phthalic acid administration.

Overall, the assessment of Dr. Joseph was that the 105-week carcinogenicity study of phthalic anhydride in rats and other nonclinical studies of phthalic acid and

phthalic anhydride provide a reasonable assurance of safety for the ingestion of phthalic acid associated with Ultrase administration.

- Iron oxide is classified as a color additive for ingested drugs that may be safely used in an amount no greater than 5 mg/day of elemental iron under US regulations. The maximum daily dose of iron oxide in patients treated with Ultrase is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60 kg patient. This would be (b) (4) mg/day of elemental iron, which exceeds the limit by more than three-fold. The oral LD_{50} for iron oxide in both rats and mice was reported to be >15 g/kg. No other toxicity information is available, and therefore, the safety of the estimated maximum daily dose of iron oxide cannot be supported by the submitted nonclinical information. However, other health authorities, including the Office of Dietary Supplements in the National Institutes of Health, have recommended a daily allowance of 8 mg elemental iron in adult males and 18 mg elemental iron in adult females. In 2001, the Institute of Medicine established a tolerable upper limit of daily elemental iron intake for healthy people of 40 mg/day for age seven months to 13 years, and 45 mg/day for age 14 years and older. In addition, daily iron intake originating from food sources would be expected to exceed the 5 mg regulatory dose limit for iron oxide. Thus, based on recommendations of health authorities and the known level of daily iron consumption in the human diet, the estimated maximum daily dose of iron oxide resulting from Ultrase administration is not considered to be a safety concern. It is also noteworthy that the FDA Inactive Ingredients Database indicates that one drug product, an oral tablet formulation, contains 50 mg ferric (iron) oxide, a level that exceeds the estimated maximum daily dose of iron oxide for Ultrase, and another product has 13 mg of red iron oxide. Thus, there are at least two approved oral formulations for which the regulatory dose limit of elemental iron from iron oxide is exceeded.

The Applicant also submitted a published report of a special toxicology study of porcine PEP administration to rats that was intended to investigate the underlying mechanism of fibrosing colonopathy. The results of this study showed that high dose levels of PEPs produced injury in the small intestine under conditions of increased intestinal permeability induced by treatment with oleic acid and/or reserpine. CF patients are known to have high intestinal permeability; however the lesions seen in rats in this study were limited to muscle necrosis in the ileum and jejunum, which differ from those of fibrosing colonopathy. Fibrosing colonopathy lesions are characterized by submucosal fibrosis of the colon and rectum, and colonic strictures, lesions that were not observed in the intestines of the rats in this study.

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 Ultrase administration, and that an approval of the Ultrase NDA is recommended. Dr. Joseph additionally recommended that the proposed labeling be revised as follows:

- Under the Indications and Usage section of the Highlights section of the labeling, "pancreatic enzyme preparation digestant" is recommended as the established pharmacologic class.

- In the 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." The use of "pancrelipase" instead of "Ultrase MT Capsules" (as proposed by the Applicant) is recommended 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).

- In the 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", since the Applicant's version was felt to be inaccurate.

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

IV. Clinical Pharmacology

The clinical pharmacology data have been extensively reviewed by the Clinical Pharmacology Reviewer (Tien-Mien Chen, Ph.D.). Please refer to this review for more detailed information. Clinical pharmacology information submitted in the NDA submission is limited to the results obtained in a single, bioavailibility (BA) study UMT20CP05-01 (CP-01). The Applicant also submitted the results of an *in vitro* stability study (RE-071211-01; Stability Study) of Ultrase TbMP sprinkled on food. Dr. Chen's review is limited to the review of these two studies.

A. Bioavailability Study

The bioavailability (BA) study was a single-center, randomized, open-label, 2 X 2 cross-over, intubation study that evaluated the intra-duodenal delivery of lipase from two enteric-coated capsule formulations of Ultrase: the older formulation of Ultrase coated with Eudragit (Ultrase-Eudragit), which is not intended for marketing, and Ultrase coated with HP-55 (Ultrase TbMP), which is the intended to-be-marketed product. Twenty (20) adult chronic pancreatitis patients with EPI (CPPI; n=10) and without EPI (CP; n=10) were enrolled in the study. During the study, patients were confined to the research facility for a period of five to six days. The study procedures are as follows:

- On Day 1 after an overnight fast, patients were intubated using a modified Dreiling double-lumen intestinal tube. Patients were administered metoclopromide and local

anesthetics (benzocaine and lidocaine) for facilitation of tube placement, and tube position was verified by fluoroscopy. Intra-duodenal perfusion was then started with normal saline, and 10 uCi/L ^{14}C-polyethylene glycol (PEG) was used as a non-absorbable duodenal marker. The first half-hour perfusion was considered a steady-state period with no aspirations collected. Following the second half-hour of perfusion, aspirations were collected, which were considered as the washout. Following the third half-hour perfusion, aspirations were collected that were considered as Baseline samples.

- Perfusion and aspiration were then stopped for 20 minutes, and all patients received a liquid meal of Ensure Plus 500 mL. Patients received two capsules (total 46,000 USP U lipase) of either Ultrase formulation in the middle of the liquid meal during each treatment arm. Intra-duodenal perfusion was restarted after completion of consumption of the Ensure Plus, and continuous 15-minute intraluminal aspirations were then collected during the two hours post-dosing. At the end of the study, the stomach was aspirated for residual enzyme and ^{14}C-PEG.

- After a washout period of one day, patients were again fasted after midnight, and the treatment procedures were repeated using the alternate Ultrase formulation. The activity or amount of enzymes released at the site of action (duodenum) was quantified (in terms of lipase) and compared between the two formulations.

Of the 20 patients enrolled in the study, 11 patients (6 CPPI and 5 CP patients) had evaluable data. The results show:

- In CPPI patients (n=6), Ultrase TbMP had higher mean percent recovery than did Ultrase-Eudragit (43% vs. 27%, respectively). Both formulations exhibited large inter-patient variations.

- In CP patients (n=5), the opposite results were shown. That is, Ultrase-Eudragit had a higher mean percent recovery than Ultrase TbMP (260% vs. 141%, respectively). The greater than 100% recovery of lipase activity in CP patients could be due to endogenous human lipase at Baseline and the secretion of endogenous human lipase upon food stimulation. The assay was unable to differentiate between endogenous human lipase and exogenous lipase after Ultrase capsule administration.

- Both formulations exhibited high variability.

- The 90% CIs for the ratio of Ultrase-Eudragit vs. Ultrase TbMP in CPPI patients, CP patients, and for all patients combined was assessed, and none of the comparisons demonstrated comparable recovery from duodenal aspirations. The results are summarized in the following table (electronically copied and reproduced from Dr. Chen's review):

Table 2: BA Study, 90% CIs for the ratio of Ultrase-Eudragit vs. Ultrase TbMP (HP-55)

	Eudragit LD30 (Ref; old formulation)	HP55 (Test; current formulation)	Point Estimate	90% CIs (Test/Ref)
Patients	**Mean Recovery (%) of Lipase**			
CPPI* (n=6)	27.3	42.6	1.490	0.628 – 3.532
CP (n=5)	260.	141	0.540	0.180 – 1.624
Overall (n=11)	133	87.5	0.949	0.507 – 1.777

Limitations in the study were noted, including:

- For both groups of patients, the study methodology may not have reflected the actual bioavailability of the products, because complete duodenal aspiration could not be assured.

- Because of the assay limitations (unable to differentiate between endogenous human lipase and exogenous lipase), data from CP patients could not be used for the purpose of establishing comparability of Ultrase-Eudragit and Ultrase TbMP.

- For the remaining six CPPI patients, due to the small sample size and variability of the results, the data were inadequate for establishing comparability of the two formulations.

Dr. Chen's conclusion for the BA study was that comparability of the two Ultrase formulations was not demonstrated in this study.

B. *In Vitro* Stability

The *in Vitro* Stability Study was performed with the objective of demonstrating the *in vitro* stability of the minitablets (contents of the Ultrase 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 Ultrase 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 Ultrase TbMP after opening the capsules and mixing the contents (minitablets) in soft acidic foods when intact capsules cannot be swallowed.

C. Conclusions

Dr. Chen's overall conclusion was that comparability of the two Ultrase formulations was not demonstrated in the BA study. The approvability of the Ultrase TbMP was deferred to the medical review based on the clinical findings from the pivotal clinical study performed with Ultrase TbMP.

Dr. Chen additionally stated that the results from the *in vitro* stability study support the labeling of Ultrase TbMP for administration after opening the capsules and mixing the contents (minitablets) in soft acidic foods when intact capsules cannot be swallowed. Labeling recommendations were made in the Clinical Pharmacology review; however, since this NDA is recommended for an Approvable action, no labeling negotiations were undertaken during this review cycle.

V. Clinical/Statistical

The clinical data have been extensively reviewed by the Clinical Reviewer (Joanna Ku, M.D.) and the Statistical Reviewer (Stella Grosser, Ph.D.). Please refer to the Clinical and the Statistical Reviews for more detailed information.

Ultrase and Ultrase MT have been extensively used clinically as commercially available products in many countries throughout the world, and Ultrase's long-term efficacy and safety is assumed. Per the Guidance, only short-term safety and efficacy studies were performed in support of this NDA.

A. Clinical Studies

The NDA submission contains efficacy and safety information from one short-term clinical safety and efficacy study (UMT20CF05-01; CF-01; Pivotal Study) in which the Ultrase to-be-marketed product (TbMP) was administered to pediatric and adult patients with CF, two supportive short-term clinical safety and efficacy studies (96-01 and 96-02) in which an older formulation of Ultrase (Eudragit formulation) was administered to pediatric and adult patients with CF, and one clinical bioavailability (BA) study (UMT20CP05-01; CP-01; BA Study) in adult patients with chronic pancreatitis (CP). Two additional open-label clinical studies, Study 01 and Study 02, were also submitted; however, these studies were not amenable to substantive review, and were considered only for supportive safety information by the Medical Reviewer. The most important clinical study for demonstrating efficacy was the Pivotal Study (CF-01). The Pivotal Study conducted with Ultrase TbMP, and the two supportive efficacy and safety studies (96-01 and 96-02) conducted with Ultrase-Eudragit formulation are described as follows:

1. Study UMT20CF05-01 (Pivotal Study; Study CF-01) was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of Ultrase TbMP administered to 31 patients with CF and EPI, ages 8 to 37 years. The objectives of the study were to describe the short-term (approximately 40 to 50 days of Ultrase TbMP treatment) efficacy and safety of Ultrase TbMP. Efficacy was assessed by the difference in a 72-hour fecal fat collection (CFA) during Ultrase TbMP treatment as compared to placebo treatment.

2. Study 96-01 was a multi-center, randomized, DB, placebo-controlled, two-treatment, cross-over study of Ultrase-Eudragit administered to 31 patients with CF and EPI, ages 7 to 36 years. The objectives of the study were to describe the short-term efficacy and safety of Ultrase-Eudragit. Efficacy was assessed by the

difference in a 72-hour fecal fat collection (CFA) during Ultrase-Eudragit treatment as compared to placebo treatment. This study was completed in 1998, and was performed using the higher strength Ultrase-Eudragit capsules Ultrase MT20. This formulation is not being considered for marketing in the US.

3. Study 96-02 was a multi-center, randomized, DB, placebo-controlled, two-treatment, cross-over study of Ultrase-Eudragit administered to 26 patients with CF and EPI, ages 8 to 36 years. The objectives of the study were to describe the short-term efficacy and safety of Ultrase-Eudragit. Efficacy was assessed by the difference in a 72-hour fecal fat collection (CFA) during Ultrase-Eudragit treatment as compared to placebo treatment. This study was completed in 1999, and differs from Study 96-01 in that this study was performed using the lower strength Ultrase-Eudragit capsules Ultrase MT12. This formulation is also not being considered for marketing in the US.

The Clinical Reviewer (Dr. Ku) extensively reviewed the efficacy and safety information from the Pivotal Study (CF-01) only, and the Statistical Reviewer (Dr. Grosser) also conducted statistical analyses of the efficacy results from the Pivotal Study only. In addition, Dr. Ku also briefly reviewed the available safety and efficacy data from the two supportive studies, and the safety data from the BA study (the efficacy review for the BA study was deferred to the Clinical Pharmacology Reviewer Dr. Chen; see Section IV, above).

B. Efficacy Results

The primary efficacy endpoint in the Pivotal Study CF-01, and the supportive studies (96-01 and 96-02) was the comparison of percent coefficient of fat absorption (%CFA) to a %CFA on no-active (placebo) treatment. %CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet, and is calculated by:

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

A change in %CFA of 30% or greater in severely-affected patients (patients with a no-treatment %CFA of 40% or less) is considered to be clinically meaningful. No accepted change in %CFA has been established for patients with no-treatment %CFA greater than 40%. Change in %CFA with active treatment is expected to be larger in more severely affected patients than in patients with higher no-treatment %CFAs, as the more severely affected patients have a greater capacity to respond to treatment. Thus, the overall (mean) results of the studies are expected to be at least partly dependent on the severity of patients (by no-treatment/placebo %CFA at Baseline) enrolled in the studies.

1. Pivotal Study: Study CF-01

The Pivotal Study CF-01 was a multi-center, randomized (1:1 to treatment sequence), DB, placebo-controlled, two-treatment, cross-over study of Ultrase TbMP administered to 31 patients with CF and EPI, ages 8 to 37 years. The objectives of the study were to describe the short-term (approximately 40 to 50 days of Ultrase TbMP treatment) efficacy and

safety of Ultrase TbMP. The primary efficacy endpoint was the difference in a 72-hour fecal fat collection (CFA) during Ultrase TbMP treatment as compared to placebo treatment.

Ultrase TbMP was administered to all patients in the study in a dose range that complied with Cystic Fibrosis Foundation (CFF) guidelines[3] (i.e., doses of Ultrase TbMP were not to exceed 2,500 lipase units/kg/meal or 10,000 lipase units/kg/day, for three meals and two snacks per day; snack-dose is half the meal-dose of PEP). Only the Ultrase MT20 (23,000 U lipase) and Ultrase MT18 (20,700 U lipase) capsules were used in this study, and per-patient doses were obtained by rounding the dose to the nearest capsule (based on lipase units).

The study design consisted of the following periods:

- Screening Period (up to 11 days): While undergoing Screening procedures, patients who were on Ultrase MT18 or MT20 capsules were continued on their usual treatment (open-label). Patients on enzyme preparations other than Ultrase MT18 or MT20 were switched to open-label treatment with Ultrase MT20 at study entry, and received dose adjustments as necessary while consuming their usual diets. Only eligible patients (by Screening/entry criteria) were entered into the study.

- Stabilization Period 1 (up to 4 days): Open-label period during which all patients received Ultrase TbMP and were begun on a high-fat diet. The dose of Ultrase TbMP was adjusted for the increased fat intake based on clinical signs and symptoms (e.g., frequency of bowel movements). The stabilized dose was determined by the Investigator from the average dose received by the patient in the last two days of the Stabilization Period. The stabilized dose was the dose administered during the two Treatment Periods and Stabilization Period 2.

- Study Drug Treatment Period 1 (6 to 7 days): On the first day of Treatment Period 1, patients were randomized to receive either DB placebo or Ultrase TbMP (the dose of Ultrase TbMP was determined during Stabilization Period 1). The first 72-hour stool collection for CFA was collected on Days 3 to 6 (or 7, if needed) of this period.

- Break Period (3 to 6 days): Patients were free to follow their normal diets during this period, and received open-label Ultrase MT20 at an *ad lib* dose during the Break Period. No study-related assessments (e.g., food intake) were recorded during this period.

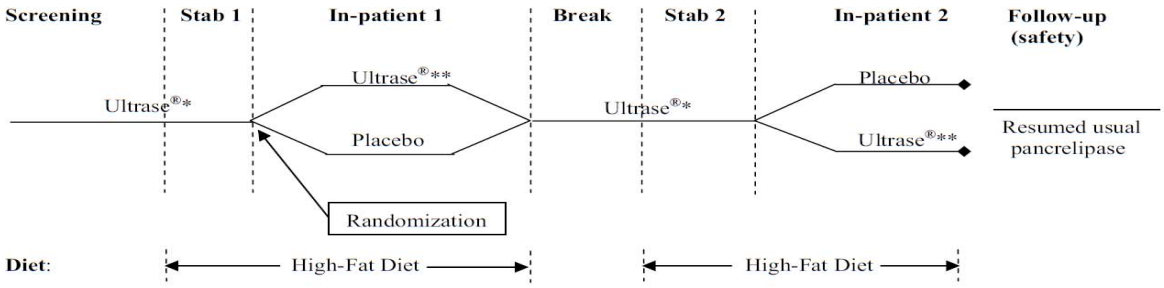
- Stabilization Period 2 (up to 4 days): Open-label period during which all patients resumed Ultrase TbMP (dose determined during Stabilization Period 1) and a high-fat diet.

[3] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with Cystic Fibrosis. J Pediatr Gastroenterol and Nutr 2002;35(3):246-259.

- Study Drug Treatment Period 2 (6 to 7 days): Patients received the alternate DB treatment during this Treatment Period (patients who received placebo in Treatment Period 1 received Ultrase TbMP during Treatment Period 2, patients who received Ultrase TbMP during Treatment Period 1 received placebo during Treatment Period 2). The second 72-hour stool collection for CFA was collected on Days 3 to 6 (or 7) of this period. A follow-up safety contact (either in person or by telephone) was made seven to ten days after completion of Day 7 of Treatment Period 2.

The overall study design is represented graphically in the following figure (electronically copied and reproduced from the Applicant's submission):

Figure 1: Pivotal Study CF-01, Overall Study Design



* Ultrase® = Commercial Ultrase® MT18 or MT20 or open-label Ultrase® MT20 from Axcan (during Screening). Open-label Ultrase® MT20 from Axcan (during Stabilization Period and Break Period).

** Ultrase® = Double-blind study drug
Note: Stab = Stabilization

The results of the study show that 36 patients were screened, and all 36 patients were exposed to Ultrase (safety population). Of these 36 patients, 32 patients were enrolled, 31 were randomized into the study, and five were screen failures (three were discontinued for SAEs, including three CF-related pulmonary events, one withdrew consent, and one did not qualify for the study [failed fecal elastase <100 criterion]). 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. Five of the 31 ITT patients withdrew prior to completing the study, including one patient who withdrew consent, one patient who was withdrawn by the Investigator (inclusion/exclusion criteria protocol violation, patient had undergone colectomy), two patients who experienced SAEs (abdominal and cough/fever), and one patient who experienced an AE (abdominal pain, anorexia, flatulence, and steatorrhea). Eighteen (18) patients completed both treatment periods of the study and had no protocol violations/major deviations. These patients constituted the Per Protocol population.

Fourteen (14) patients were randomized to treatment sequence 1 (Ultrase TbMP → placebo), and 17 patients to treatment sequence 2 (placebo → Ultrase 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 Ultrase TbMP treatment was 89%. The difference in mean CFA on Ultrase TbMP as compared to placebo was 34%, which was a clinically meaningful and statistically significant difference (p<0.0001). There were no sequence or period effects seen for these results. The results are summarized in the following table (electronically copied and reproduced from the Applicant's submission).

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

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
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	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-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.				

The primary efficacy endpoint was also analyzed by the FDA Statistical Reviewer (Dr. Grosser), whose results matched the descriptive statistics, but the inferential statistics differed by a small amount (<10%), which did not change the overall findings. Dr. Grosser additionally notes that the Applicant's analysis of the primary endpoint was an observed-case analysis, where dropouts were not replaced and missing observations were not imputed. Five of the 30 patients during Ultrase treatment and four of the 31 patients during placebo treatment did not have CFA results, and seven patients did not have measurements at the end of both periods and were, therefore, missing values of the Delta (Ultrase - placebo CFA result). Dr. Grosser stated that when the smallest observed Delta (-7.24) was imputed for the seven missing values, the mean change decreased from 34.7% (observed-case result) to 24.3%. While this value is considerably smaller than the observed mean, it is still highly significantly different from zero, implying that the missing values would be unlikely to change the conclusion of a significant treatment effect.

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 no-treatment CFA subgroups of severely-affected (CFA ≤40%), moderately-affected (>40 and ≤80%), and mildly-affected (>80%). The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of ≤40%; there are no generally accepted definitions for moderately- and mildly-affected patients, and these cut-points were arbitrarily selected. In severely-affected patients, an increase in CFA of ≥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 showed that for the severely-affected patients (n=6), the mean CFA during placebo treatment was 24%, mean CFA during Ultrase TbMP treatment was 89%, and the mean difference on Ultrase 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 Ultrase treatment was 87%, and the mean difference on Ultrase 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 Ultrase treatment was 92%, and the mean difference on Ultrase as compared to placebo was 3%. This difference is not 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 Ultrase treatment correlated strongly with placebo-CFA. That is, patients with lower CFA while on placebo had the greatest increases in CFA on Ultrase treatment, and those with higher placebo-CFA had smaller changes. These results are consistent with a clinically meaningful treatment benefit with Ultrase treatment in patients with moderate to severe no-treatment CFA.

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. The Statistical Reviewer noted that the small sample size of the study did not allow for meaningful statistical comparisons of the subgroups.

Overall, the results for the primary endpoint show that treatment effect tends to have a linear relationship with the no-treatment (placebo) condition of the patient. That is, patients who were more severely affected (lower no-treatment/placebo CFA) tended to have higher increases in CFA on Ultrase treatment. This result is consistent with a clinically meaningful treatment benefit with Ultrase in patients with moderate to severe no-treatment CFA. This result is also consistent with the previous experience with the PEPs as described in the medical literature, since patients with a lower CFA on no-treatment have a higher capacity to respond to treatment. No other factors were identified in this study that appeared to have an effect on response, including treatment sequence, age, or gender.

Limitations in this study include the small numbers of patients included in the study, and the small number of patients in the severely-affected (n=6) subgroup.

Despite the limitations of the study, the results demonstrate a statistically significant and clinically meaningful benefit to treatment with Ultrase TbMP in patients with EPI due to CF, ages 8 to 37 years, and support the approval of Ultrase TbMP for the treatment of steatorrhea due to EPI.

2. Supportive Studies 96-01 and 96-02

The two supportive studies 96-01 and 96-02 were nearly identical in design, both being multi-center, randomized (1:1 to treatment sequence), DB, placebo-controlled, two-treatment, cross-over studies of Ultrase-Eudragit administration, and the design was similar to the design used in the Pivotal Study (CF-01). Both studies were completed more than ten years ago and used a different formulation of Ultrase than the Ultrase TbMP, with the formulations differing predominantly by the delayed-release coating of the Drug Product. Since comparability between the two formulations has not been demonstrated (in the BA study), the results of studies 96-01 and 96-02 cannot be used to provide primary evidence of efficacy (and safety) of Ultrase TbMP, and thus, will be used only as supportive evidence of efficacy (and safety).

The objectives of the studies were to describe the short-term efficacy and safety of Ultrase-Eudragit administered to a total of 57 patients with CF and EPI, ages 7 to 36 years. The primary efficacy endpoint was the difference in a 72-hour fecal fat collection (CFA) during Ultrase-Eudragit treatment as compared to placebo treatment. The two studies differed in that a higher-strength Ultrase-Eudragit capsule (Ultrase MT20) was administered in Study 96-01, and lower-strength Ultrase-Eudragit capsule (Ultrase MT12) was administered in Study 96-02.

The results for Study 96-01 showed that 31 patients were randomized, and 27 patients completed Treatment Period 1 (either placebo or Ultrase-Eudragit treatment, depending on randomization sequence): 14 patients were randomized to the treatment sequence Ultrase-Eudragit → placebo, and 13 patients to placebo → Ultrase-Eudragit. Twenty-five (25) patients completed both treatment periods of the study (i.e., had CFA results during both the placebo and Ultrase-Eudragit treatment periods). Patient ages ranged from 7 to 36 years, 70% of patients were male, and 96% were Caucasian.

The primary efficacy endpoint results showed that the mean CFA on placebo treatment (n=25) was 59%, and the mean CFA on Ultrase-Eudragit treatment (n=27) was 88%. The mean difference between the treatment periods was 29%, which was highly statistically significant (p=0.0001). The results were not confirmed by the FDA Statistician. The Applicant's results are summarized in the following table (electronically copied and reproduced from the Applicant's submission).

Table 4: Study 96-01, Primary Efficacy Endpoint Results (CFA%)

OVERALL SUMMARY OF PERCENT ABSORPTION – INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=27)** [1]	**Placebo (N=25)**	**Treatment Comparison (p-value)**
Dietary Fat (g)			
Mean ± SD	87.7 ± 10.1	58.7 ± 16.5	0.0001*
Range	46.8 to 99.1	29.9 to 96.2	
N	26	25	

The results for the Study 96-02 showed that 26 patients were randomized, and 23 patients completed Treatment Period 1 (either placebo or Ultrase-Eudragit treatment, depending on randomization sequence): 12 patients were randomized to Ultrase-Eudragit → placebo, and 11 patients to placebo → Ultrase-Eudragit. Twenty-two (22) patients completed both treatment periods of the study. Patient ages ranged from 8 to 36 years, 70% of patients were male, and 87% were Caucasian.

The primary efficacy endpoint results showed that the mean CFA on placebo treatment (n=22) was 47%, and the mean CFA on Ultrase-Eudragit treatment (n=23) was 79%. The mean difference between the treatment periods was 33%, which was highly statistically significant (p=0.0002). The results were not confirmed by the FDA Statistician. The Applicant's results are summarized in the following table (electronically copied and reproduced from the Applicant's submission).

Table 5: Study 96-02, Primary Efficacy Endpoint Results (CFA%)

OVERALL SUMMARY OF PERCENT ABSORPTION FOR INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=23)**	**Placebo (N=22)** [1]	**Treatment Comparison (p-value)**
Dietary Fat (g)			
Mean ± SD	79.4 ± 12.5	46.7 ± 35.8	0.0002*
Range	49.7 to 95.9	-51.3 to 90.5	
N	23	22	

These results show a significant difference in favor of Ultrase-Eudragit treatment for mean change CFA as compared to placebo treatment. These results are supportive of the efficacy of Ultrase in the treatment of steatorrhea due to EPI in patients 7 years of age and older.

3. Efficacy Conclusions

The efficacy findings from the pivotal short-term efficacy and safety study conducted with Ultrase TbMP, and from the two supportive studies conducted with Ultrase-Eudragit show that:

- In the Pivotal Study, the treatment of pediatric and adult patients with CF and EPI, ages eight years and older, with Ultrase TbMP results in a statistically significant and clinically meaningful benefit to patients, as shown by mean increases in CFA during Ultrase TbMP treatment as compared to placebo treatment. Subgroup analysis showed that severely-affected patients (patients with CFA less than 40% on

placebo treatment) had the greatest increases in CFA on Ultrase TbMP treatment. These results are consistent with results seen with other PEPs, and are supportive of the labeling of Ultrase TbMP for the treatment of steatorrhea in patients with EPI due to CF and other causes, ages eight years and older.

- Supportive evidence of the efficacy of Ultrase was shown in two supportive studies in which a different formulation of Ultrase (Ultrase-Eudragit) was administered. These studies showed mean increases in CFA of 29% (Study 96-01) and 33% (Study 96-02) while on Ultrase-Eudragit treatment as compared to placebo treatment, which were statistically significant. However, comparability between the two Ultrase formulations was not demonstrated in the BA study, and therefore, these results cannot be used to provide primary evidence of efficacy for Ultrase TbMP.

- Children younger than seven years of age were not studied in the clinical development program for Ultrase TbMP. Since pediatric patients aged one month and older will almost certainly be administered Ultrase for the treatment of EPI in the post-marketing period (should Ultrase be approved), the Applicant will need to assess the efficacy and safety of Ultrase administration to younger patients. The Applicant has requested a deferral for conducting studies in patients less than two years of age until the post-marketing period, as the Applicant is developing a pediatric formulation suitable for administration to younger patients who are unable to swallow intact capsules. The Division feels that this deferral request is reasonable.

Overall, these efficacy findings support the approval and labeling of Ultrase TbMP for the treatment of steatorrhea due to EPI from CF or other causes, in pediatric and adult patients, ages seven years and older.

C. Safety Results

1. Background

Porcine-derived PEPs have been in clinical use since prior to 1938, and there is extensive clinical experience with these products in human patients. This long-term safety experience has demonstrated that the PEPs are relatively safe, and the PEPs' Adverse Event (AE) profile has been well described in the clinical literature. The clinical benefits of PEP treatment in some populations have also been established, such as pediatric patients with CF, who have been shown to do better clinically over the long-term with PEP administration (i.e., gain weight, maintain growth, and have fewer disease-related complications). In consideration of this long and extensive safety experience with the PEPs, the Guidance assessed that it is not necessary to conduct long-term safety evaluations of the PEPs in support of the PEP NDAs; however, short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the Gastrointestinal (GI) tract and are not absorbed, the Guidance further recommended that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms (i.e., AEs) during these clinical trials.

One exception to the relative safety of the PEPs is the association of fibrosing colonopathy with PEP use. Fibrosing colonopathy associated with PEP use is rare, and most of the cases of fibrosing colonopathy have been reported in younger children with CF. Although the etiology has not been completely elucidated, fibrosing colonopathy is thought to be related to high or inappropriate dosing of PEPs, or may result from excipients or from the release of enzymes in the colon with treatment with the delayed-release PEP formulations. In consideration of the potential risk to patients of high-dose PEP administration, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA have published guidelines that recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal (FitzSimmons et al., 1997[4]; Borowitz et al., 2002[3]). Since publication of these recommendations, cases of fibrosing colonopathy have been reported only sporadically. Given the rarity of fibrosing colonopathy, cases are unlikely to be reported during the relatively small clinical trials conducted in support of the PEP NDAs, and continued monitoring for fibrosing colonopathy associated with PEP use is likely to best be performed through global safety surveillance.

Consistent with the Guidance, the safety evaluations performed for the Ultrase clinical development program focused predominantly on the monitoring of clinical signs and symptoms (i.e., AE assessments) during the short-term clinical efficacy and safety studies conducted with Ultrase, and no long-term safety studies were performed.

2. Safety Review

The safety information submitted in this NDA submission includes an Integrated Summary of Safety (ISS), and safety information from three individual clinical studies conducted with Ultrase (CF-01, 96-01 and 96-02). Thus, the submitted safety information consists of safety assessments obtained with both the Ultrase TbMP and Eudragit formulations. The most important safety information available for review in the NDA submission was the safety data obtained from the Pivotal Study CF-01, which was performed with Ultrase TbMP. The Medical Reviewer analyzed the safety information from the Pivotal Study separately, and also pooled the electronic safety datasets for the three studies (CF-01, 96-01 and 96-02) so as to perform an independent review of the safety data contained in this NDA submission. The 120-Safety Update was also submitted during the review cycle (dated 01-February-2008), and the results were integrated by the Medical Reviewer in the overall safety analysis.

Ultrase is a marketed product that has been commercially available in the US since 1991. Ultrase is also available in a number of countries throughout the world, such as Canada, and several countries in South America since at least 1999; however, the majority of the patient exposure to Ultrase is from the US (accounting for approximately (b)(4)% of Ultrase global sales). This marketing experience includes exposure to both the Ultrase TbMP and Ultrase-Eudragit formulation. The post-marketing safety experience has also been

[4] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with Cystic Fibrosis. N Engl J Med 1997;336:1283-1289.

summarized by the Applicant from their pharmacovigilence database, and has been reviewed by the Medical Reviewer as part of the safety review.

Safety information (predominantly AE collection) was also obtained in the BA study that was of limited utility given the design of the study and the small numbers of patients exposed to two, single-doses of Ultrase in this study. Additional safety information provided in the legacy reports from the two oldest studies (Study 01 and 02) conducted with Ultrase-Eudragit was also submitted in the NDA; however, the safety data were not amenable to independent, substantive review, and the Medical Reviewer did not include these data in the analysis, nor did the Applicant include these studies in the ISS.

3. Results

a) Exposure

The total patient exposure included in the safety evaluation of Ultrase was 88 patients from the three clinical trials. Exposure included:

- Pivotal Study (CF-01): Multiple-dose (5-times a day for approximately 40 to 50 days) administration to 31 pediatric and adult patients with CF, ages 8 years through adults, including:
    - Ages 8 to 11 years: 2 patients
    - Ages 12 to 16 years: 10 patients
    - Ages >16 years: 19 patients

- Study 96-01: Multiple-dose (5-times a day for approximately 30 days) administration to 31 pediatric and adult patients with CF, ages 7 years through adults. The Applicant states that the numbers of patients by age group in this study included:
    - Ages 7 to 11 years: 5 patients
    - Ages 12 to 16 years: 10 patients
    - Ages >16 years: 16 patients

- Study 96-02: Multiple-dose (5-times a day for approximately 30 days) administration to pediatric and adult patients with CF, ages 8 years through adults. The Applicant states that the numbers of patients by age group in this study included:
    - Ages 8 to 11 years: 7 patients
    - Ages 12 to 16 years: 7 patients
    - Ages >16 years: 12 patients

Demographic data for the patients included in the safety analysis and the study designs for these three studies were similar, and the data were amenable to pooling. Overall, there was a male predominance (approximately 70%), mean age was about 17 years, and 93% of patients were Caucasian. The predominance of Caucasians in the study is consistent with the ethnic prevalence of CF in the US, but the reason for the male predominance in an autosomal recessive disease is unclear. The demographic data for all randomized patients in the three pooled studies are summarized in the following table (electronically copied and reproduced from the Applicant's submission).

Table 6: Demographic data for Studies CF-01, 96-01, and 96-02

Variable	Study	96-01 n=31*	96-02 n=26*	UMT20CF05-01 n=31*
Age (years)	mean (SD)	16.9 (6.6)	16.5 (6.5)	19.6 (6.6)
	range	7.0 - 36.0	8.0 – 36.0	8 - 37
Weight (kg)	mean (SD)	50.9 (17.5)	49.8 (14.7)	55.56 (11.61)
	range	19.0 - 91.0	26.8 – 80.0	31.1 - 88.0
Height (cm)	mean (SD)	158.6 (18.1)	157.8 (16.1)	164.3 (13.2)
	range	113.0 – 183.0	127.0 – 185.4	1.22 - 1.89
Years since CF diagnosis	mean (SD)	16.2 (6.8)	15.9 (6.4)	19.2 (7.4)
	range	4.0 – 35.0	6.0 – 33.0	3 - 37
Gender, n (%)	male	23 [74]	17 [65]	20 (64.5)
	female	8 [26]	9 [35]	11 (35.5)
Race, n (%)	Caucasian	30 [97]	22 [85]	29 (93.5)
	Black	0	2 [8]	2 (6.5)
	Hispanic	1 [3]	1 [4]	0
	Caucasian/Black	0	1 [4]	0

*All randomized patients

Exposure to study medication in the three pooled studies was also similar, with mean exposure ranging from about 6,900 to 7,600 U lipase/day. The estimated exposure by dose (based on lipase units) by study is summarized in the following table (electronically copied and reproduced from the Applicant's submission).

Table 7: Ultrase Exposure (lipase units) for Studies CF-01, 96-01, and 96-02

Study	n	Mean (SD)	Range
96-01	27 (ITT population)*	7638.62 (3472.34)	1061.26 - 17610.10
96-02	23 (ITT population)*	6920.62 (2707.58)	2656.83 - 10809.20
UMT20CF05-01	30 (Safety population)**	7534.20 (2732.18)	2483.80 - 12419.01

* in study 96-01, 4 of 31 patients did not complete at least one treatment period; in Study 96-02, 3 of 26 patients did not complete at least one treatment period

** safety population who received at least one dose of ULTRASE® treatment. Estimated mean calculated as mean capsules per day (n=30) x 23,000 lipase units per capsule x mean weight of population (n=31).

Source: 5.3.5.1 Study 96-01, Vol. 3, p. 42; Study 96-02, Vol. 7, p. 44; Study UMTCF05-01, Vol. 11, p. 66

Single-dose 46,000 U lipase (~750 U/kg for a 60 kg patient) administration to 11 adult patients with CP was performed in the BA study. Post-marketing exposure was also estimated to be about 50,000 patient-years of exposure from 2000 to 2007 at a variety of doses administered.

b) Safety Findings

The AE profile of Ultrase as described in the three pooled 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 safety review.

In the Ultrase clinical development program there were no deaths, and a total of eight patients reported at least one Serious Adverse Event (SAE) during any of three studies. The SAEs tended to reflect underlying disease, and none were attributed as being related to study drug treatment. The SAEs are summarized as follows:

- In the Pivotal Study CF-01, five patients reported SAEs, including one patient who experienced a CF-related pulmonary exacerbation (acute bronchiectasis) during placebo treatment, two patients who experienced either a CF-related pulmonary exacerbation or hemoptysis during Ultrase TbMP use in the Screening period, and two patients reported SAEs after resuming their usual PEPs during the follow-up period (after Treatment Period 2), including pulmonary and GI complaints (dyspnea, cough, chills, nausea, vomiting and abdominal pain) in one patient, and CF-lung, hypokalemia and lymphadenopathy in the other.

- In Study 96-01, three patients reported SAEs, including two patients who experienced either abdominal cramping or CF-related pulmonary exacerbation while on placebo, and one patient who was diagnosed with diabetes mellitus (DM) during Ultrase-Eudragit treatment.

Discontinuations from the studies due to AEs (SAEs and non-serious AEs) included a total of 11 patient discontinuations from the three studies. None of the AEs were attributed as being related to study drug treatment. The AEs resulting in study discontinuation are summarized as follows (the SAEs resulting in discontinuations are also summarized in the SAE paragraph above):

- In the Pivotal Study CF-01, three patients were discontinued for SAEs, and two patients for AEs including: two patients during the Screening period for SAEs while on Ultrase (pulmonary exacerbation and hemoptysis), one patient during the Break Period while on open-label Ultrase (including the preferred terms CF-lung, bronchiectasis, upper respiratory tract infection, GI infection, vaginal infection, and malnutrition), and two patients for non-serious AEs while taking placebo (including the preferred terms of abdominal pain, flatulence and steatorrhea).

- In Study 96-01, three patients withdrew due to SAEs, including: one patient for intestinal obstruction while on placebo, one patient for cough while on open-label Ultrase during Screening, and one patient diagnosed with DM during Ultrase treatment.

- In Study 96-02, three patients withdrew due to non-serious AEs while on placebo, including one patient each for intestinal obstruction, intestinal disorder, and rectal disorder.

For events of particular concern to this (and any other PEP) clinical development program, including fibrosing colonopathy, hyperuricemia and hyperuricosuria, there were no cases of fibrosing colonopathy, hyperuricemia or hyperuricosuria reported. This result is not unexpected given the rarity of fibrosing colonopathy, the small size of the safety population, and the limited duration of study drug treatment.

Review of the safety information in the three pooled studies (n ~88) showed that the most commonly reported AEs were in the GI and respiratory systems, which is consistent with the underlying condition of the patients. By preferred term, the most commonly reported AEs were abdominal pain (reported by 17% of patients taking Ultrase and 50% taking placebo), flatulence (26% Ultrase, 44% placebo), diarrhea (10% Ultrase, 15% placebo), and headache (11% Ultrase, 6% placebo). The majority of AEs were mild to moderate in severity. The types of AEs reported during Ultrase and placebo treatments were similar; however, it appears that GI AEs occurred at higher rates during placebo treatment, which is consistent with unmasking of the underlying condition of the patients while they were not receiving active PEP treatment.

A similar AE profile of Ultrase TbMP as compared to pooled Ultrase (both formulations) was seen when the AEs reported in the Pivotal Study CF-01 were analyzed separately. In the Pivotal Study, the majority of AEs were reported in the GI (and Investigations SOC, which would include increased fecal fat) and respiratory systems. The most commonly reported AEs by preferred term were abdominal pain (approximately 40%) and fecal fat increase (approximately 30%). The GI AEs (and Investigations AE of increased fecal fat) were reported more commonly during placebo treatment.

The post-marketing safety findings from the Ultrase pharmacovigilence program covering the time period of January 2000 through January 2007 show exposure to Ultrase TbMP has been for approximately 50,000 patient-treatment years. The types of AEs reported are generally similar to those AEs reported in the clinical studies conducted with Ultrase; however, since post-marketing surveillance relies on voluntary reporting and the true denominator (of patients exposed) is not known, no incidence rates can be calculated for the post-marketing events.

The post-marketing safety information is notable for 11 cases of fibrosing colonopathy having been reported. These cases were reported in CF patients taking multiples PEPs, including Ultrase. A literature review conducted by the Applicant for other notable safety concerns with Ultrase and other PEPs included the events of:

- Hypersensitivity: including skin (e.g., urticaria, pruritus) and respiratory (e.g., wheezing, dyspnea) reactions, all of which are thought to be due to inhalation of the PEP powder that occurs when capsules are opened.
- Hyperuricemia and hyperuricosuria.
- Intestinal obstruction and stricture (fibrosing colonopathy).
- Other GI complaints, such as esophageal injury.

Given that these events are known to occur with PEP administration and the potential seriousness/severity of these events, these events should be included in the Precautions/Warnings sections of PEP product labeling, including Ultrase.

Thus overall, the AE profile of Ultrase is consistent with the AE profile of the PEPs as described in the medical literature, and no new or notable safety signals were identified.

D. Clinical Conclusions and Recommendations

The Clinical and Statistical Reviewers concluded that this NDA submission provides evidence of short-term efficacy for Ultrase TbMP, and the Clinical Reviewer found that the safety profile of Ultrase is acceptable for treatment of this patient population. This Reviewer is in agreement with the Clinical and Statistical Reviewers that the clinical efficacy and safety findings for the Ultrase TbMP from the Pivotal Study, the safety and efficacy information from the Ultrase clinical development program (which includes the two supportive studies conducted with Ultrase-Eudragit), and the safety findings in the post-marketing pharmacovigilence/safety surveillance program for Ultrase support the approval and labeling of Ultrase for the treatment of steatorrhea due to EPI from CF or other causes, in pediatric and adult patients, ages seven years and older.

VI. Clinical Site Inspections

Site inspections of two clinical sites were performed by the Division of Scientific Investigations (DSI) as part of the review of this NDA submission. These inspections were of the following sites, both of which participated in the Pivotal Study CF-01:

- Site #02, Investigator Theodore Liou, M.D., University of Utah School of Medicine, Salt Lake City, UT.
- Site #03, Investigator Steven Strausbaugh, M.D., Rainbow Babies and Children's Hospital, Cleveland, OH.

Important issues identified during the site inspections are summarized as follows (please see the Clinical Inspection Summary memorandum by Khairy Malek, M.D., for more detailed information on the results of the inspection).

For Dr. Liou's' site (#02):

- Seven patients were enrolled at this clinical site. The field inspector reviewed the records of all the patients in the study. There were no limitations to the inspection.

- Many protocol violations for the seven patients were noted, including:
    - Four patients were allowed in the study before getting their fecal elastase results (inclusion criterion for entry).
    - 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. In addition, three patients had poor dietary compliance during various Stabilization and Treatment periods.

- The overall assessment of the Inspector was that these violations did not affect the validity of the data or markedly affect the calculation of the CFA (primary efficacy endpoint), and that the data from this site can be used in support of the NDA.
- Due to the numerous protocol violations noted at the site, the site received a final classification for this inspection of Voluntary Action Indicated (VAI)-No Response Requested.

For Dr. Stausbaugh's site (#03):

- Six patients were enrolled at this clinical site, but only four patients completed the study (one patient discontinued for an AE, and one was discontinued for a missed stool collection). The field inspector reviewed the records of all the patients in the study, and there were no limitations to the inspection.

- There were minor protocol violations: two patients were enrolled before the results of the fecal elastase tests were received. The results were later found to be within the protocol requirement.

- The overall assessment of the Inspector was that the data from this site can be used in support of the NDA.

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.

Due to the numerous protocol violations noted at Dr. Liou's site and the VAI-No Response Requested classification, DSI sent a letter (dated 21-April-2008) to Dr. Liou notifying him that he did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. This letter emphasized that Dr. Liou did not adhere to the protocol (e.g., fecal elastase determinations were not performed prior to study enrollment), did not ensure dietary compliance of study subjects, and did not have adequate study involvement of a qualified dietician. Dr. Liou was requested to make appropriate corrections to his site procedures so that these findings would not be repeated in any ongoing or future studies.

VII. Advisory Committee

An Advisory Committee was not convened for this application.

VIII. Trade Name Review

A review of the trade name "Ultrase MT" was performed by the Division of Medication Errors Prevention (DMEP), Office of Surveillance and Epidemiology (OSE). Please see the completed consultation (by Denise Baugh) for more detailed information.

Important issues identified in the review of the proposed trade name are summarized as follows:

- DMEP considers 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.

- DMEP noted that the proprietary name Ultrase contains the USAN stem "-ase", which is inconsistent with the USAN Council's intent that USAN stems be reserved for

established names only. This was also cited by DMEP as an additional reason to object to the proposed proprietary name "Ultrase".

- 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.

- The Applicant stated that they will continue to sell the old formulations of Ultrase remaining in their inventories after approval of the new formulations, and therefore, there will be an overlap of the old and new formulations of Ultrase in the marketplace. Since the lipase, protease, and amylase components differ between the old and new formulations, but the numerical modifier remains unchanged, DMEP is concerned that this will lead to confusion and unintentional over- or under-dosing. DMEP recommends that the older formulations be removed from the market once the new formulations are approved.

A letter was sent to the Applicant during the review cycle (dated 24-June-2008) notifying the Applicant that the proposed trade name "Ultrase MT" was unacceptable and requesting submission of two alternative trade names. Thus, at the time of this review, no trade name has yet been agreed upon with the Applicant. All of the comments listed above were also delineated in the letter.

Additional labeling and label change recommendations were also included in the letter, including recommendations to improve the prominence of the proprietary name, established name and dosage form, and to clearly differentiate the net quantity from the contents per capsule. It was additionally noted that the capsule strength is inconsistent with the number of units of lipase per capsule (e.g., MT 12 capsule contains 13,800 U lipase), which could potentially increase the risk of confusion leading to medications errors.

IX. Pediatrics

Ultrase is intended for use by pediatric patients, the majority of whom have CF, and the Applicant intends to market Ultrase to pediatric patients should Ultrase receive NDA approval. A recent CFF consensus statement[3] recommends that all pediatric patients with CF be treated with PEPs as soon as CF is diagnosed, which would include the treatment of infants. Therefore, the evaluation of the safety and efficacy of Ultrase in children from infancy through adolescence in clinical trials is considered to be necessary for the adequate assessment of this product.

The overall Ultrase clinical development program has included pediatric patients in three short-term, safety and efficacy studies, which included patients ranging in age from seven through 18 years (and older); however, only one of these studies was performed with the intended to-be-marketed product (Ultrase TbMP). Overall exposure to Ultrase (TbMP and Eudragit formulations) in the clinical development program by age group is summarized as follows: 14 children ages $\geq$3 to <12 years, and 27 adolescents ages $\geq$12 to 16 years.

Pediatric patients by age subgroups and by clinical study/Ultrase formulation exposure are summarized, as follows:

- Pivotal Study (Ultrase TbMP): Approximately 12 pediatric and 19 adult (>16 years) patients with CF, ages 8 years through adults, including:
    - Ages 8 to 11 years: 2 patients
    - Ages 12 to 16 years: 10 patients
    - Ages >16 years: 19 patients

- Studies 96-01 and 96-02 (Ultrase-Eudragit): Approximately 29 pediatric and 28 adult patients with CF, ages 7 years through adults, including:
    - Ages 7 to 11 years: 12 patients
    - Ages 12 to 16 years: 17 patients
    - Ages >16 years: 28 patients

No patients less than seven years of age were evaluated in the Ultrase clinical development program; however, since children ages 2 to 11 years are usually included in this age group (children) by FDA, extrapolation of the data for labeling down to two years of age is likely reasonable. No infants (less than two years of age) have been evaluated, however. During the review cycle, the Applicant submitted a request for deferral from performing a pediatric study in infants less than two years of age, which requested that the Applicant be allowed to perform this study in the post-approval period. No study design for the infant study has yet been proposed by the Applicant.

Thus overall, pediatric patients from seven to 18 years of age were represented in the Ultrase clinical program. The efficacy and safety of Ultrase was demonstrated in pediatric patients, and pediatric patients do not appear to be respond differently to Ultrase treatment than do adults. These results support the approval and labeling of Ultrase in patients with EPI due to CF and other causes, from ages seven years (and possibly as young as two years) of age through adulthood. The Applicant plans to study patients from one month through two years of age in the post-approval period, and should Ultrase receive an Approval action in a subsequent review cycle, this study will likely be required of the Applicant as a post-marketing commitment.

X. Regulatory Conclusions

This Reviewer recommends that this NDA submission receive an Approvable action based on the large number of Drug Substance (including manufacturing and controls, and virology deficiencies), Drug Product, and packaging and final Drug Product release deficiencies noted by the CMC Review Team. The Drug Substance (DS) and Drug Product (DP) deficiencies will be communicated to the DS ((b) (4) and DP (Eurand) manufacturers in separate letters to be sent by DTP (please see Sections II.A.1. and II.A.2.of this review for a listing of the DS and DP deficiencies, respectively, and Section II.C. for a listing of the virology deficiencies). The packaging and final DP release deficiencies will be communicated by the Division to the Applicant (Axcan) in the Approvable (AE) letter.

The wording to be included in the AE letter for the packaging and final DP release deficiencies is as follows:

Chemistry, Manufacturing and Controls

1. We found that the DMFs supporting your application (DMF (b) (4) DMF 15681) are deficient. Letters stating all deficiencies will be 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.

Inspection

3. Prior to approval, an acceptable inspection of your manufacturing facilities is required.

The clinical data submitted in this NDA submission provide evidence of the short-term efficacy and safety of Ultrase for the treatment of steatorrhea in patients with EPI, ages seven years through adulthood, and are supportive of the approval and labeling of Ultrase for this indication. Since pediatric patients aged 2 to 11 years are usually included by the Agency in the "children" age group, labeling of Ultrase down to the age of two years based on the data included in this NDA submission can be considered. However, since Ultrase is likely to be used by pediatric patients as young as one month of age, should Ultrase be

approved during a subsequent review cycle, then an additional pediatric study in patients one month through two years of age (infants) will be needed. The Applicant has submitted a pediatric deferral request, and has requested that this study be performed during the post-approval period. The Division feels this request is reasonable, and will likely require this study as a condition of Approval during a subsequent review cycle (i.e., as a post-marketing commitment). Other than the deferred pediatric study, no additional clinical studies are required of the Applicant at this time.

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/s/

Anne Pariser
7/1/2008 08:57:23 AM
MEDICAL OFFICER

Daniel A. Shames
7/1/2008 12:41:48 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-222
Submission Code	N
Letter Date	31 July 2007
Stamp Date	1 August 2007
PDUFA Goal Date	1 July 2008
Clinical Reviewer	Joanna W. Ku, MD
Clinical Team Leader	Anne R. Pariser, MD
Review Completion Date	30 June 2008
Established Name	Pancrelipase, USP
(Proposed) Trade Name	Ultrase® MT capsules
Therapeutic Class	New Molecular Entity (NME)
Applicant	Axcan Scandipharm, Inc.
Priority Designation	Priority Review (P)
Formulation	Oral Capsules
Dosing Regimen	500 to 1,000 lipase USP units/kg/meal, not to exceed 2,500 USP units/kg/meal or 4,000 lipase USP units/g fat/day
Indication	Pancreatic enzyme replacement
Intended Population	Adult and pediatric patients with pancreatic enzyme deficiency due to cystic fibrosis, chronic pancreatitis, or other related disorders

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action. Deficiencies in chemistry, manufacturing and controls (drug substance and product) will need to be addressed in order to receive an Approval.

This Reviewer finds that the safety and efficacy of the to-be-marketed product (TbMP) of Ultrase® MT have been established for the treatment of steatorrhea in patients who are ages seven-years or older with exocrine pancreatic insufficiency (EPI). This is based on data from the pivotal study, Study UMT20CF05-01, in which patients with cystic fibrosis (CF) with EPI were treated with the TbMP Ultrase® MT coated with HP-55.

The two older studies conducted (Studies 96-01 and 96-02) using an older formulation of the product, Ultrase® MT coated with Eudragit®, could be used to provide supportive evidence for the safety and efficacy of Ultrase®. These older studies could be used to provide supportive—but not definitive--evidence for the safety and efficacy of the to-be-marketed product because the bridging *in vivo* bioactivity/bioavailability test failed to establish comparability between the two formulations in enzyme bioactivity/bioavailability at the physiologic site of action in the duodenum.

The Sponsor should be granted a Pediatric Deferral for infants less than two years of age to allow additional time to develop an infant-appropriate formulation. The Sponsor has been advised to conduct an additional clinical study in children between two and seven years of age should that age group be sought for inclusion in labeling.

1.2 Risk Benefit Analysis

Pancreatic enzyme products (PEPs) of porcine or bovine origin are used to treat exocrine pancreatic insufficiencies (EPI) in children and adults with cystic fibrosis (CF) and chronic pancreatitis (CP). On 28 April 2004 (69 FR 23410), the Food and Drug Administration (FDA) announced that all orally administered pancreatic enzyme products (PEPs) are new drugs that will need to be approved for prescription use only. This ruling stemmed from the concerns that although these products have been available for use more than 70 years in the United States (US), there are deficiencies in product quality and inconsistencies in enzyme bioactivity, and there is a need for continuous physician monitoring of patients who use these products as prescription medications.

The Agency has determined that there is an existing body of evidence that PEPs have clinical benefit for patients with CF and CP (69 FR 23410), in that safety and efficacy have already been established by consensus in the literature and the international medical community. Therefore, the requirement for a New Drug Approval (NDA) is less extensive and rigorous than that for a drug with less of a clinical track record. In a Guidance document for submitting NDAs of PEPs,

the Agency explained the type and amount of evidence that is required,[1] including the following discussion points, which could apply to this NDA. The duration of the entire pivotal trial could be days to two to three weeks, and the total number of patients in the study could be between 10 and 25, depending on the design chosen. One adequate and well-controlled clinical investigation and confirmatory evidence may be appropriate. A cross-over study in which each patient in the study is treated with the intended product and a control is an acceptable study design; and demonstration that administration of the PEP to patients with EPI causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection, a pharmacodynamic endpoint, is an acceptable clinical efficacy endpoint. Additionally, because CF is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with CF. Safety variables should include symptoms and signs of malabsorption, such as manifestations of steatorrhea; complaints of bloating; flatus; abdominal pain; loose and frequent stools; overt diarrhea; blood in the stool. The safety issues of uric acid elevations and fibrosing colonopathy should be addressed. This Reviewer finds that the present NDA for Ultrase® MT has satisfactorily addressed all of these issues.

The Sponsor submitted three short term clinical efficacy and safety trials of Ultrase® in patients with EPI due to CF. The pivotal study was UMT20CF05-01, in which the TbMP of Ultrase® (Ultrase® MT coated with HP55) was studied. The supporting studies were Studies 96-01 and 96-02, in which an older formulation of Ultrase® (Ultrase® MT coated with Eudragit®) was used.

The pivotal study (Study UMT20CF05-01) was a multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over study in which each patient was used as their own control. The study population comprised of 31 intent-to-treat patients who were older than seven years of age, and had EPI due to CF. Patients were randomized 1:1 to two groups, with one group undergoing one-week of treatment with Ultrase® MT 20 capsules, followed by one-week treatment with Placebo; and the other group, vice versa in their treatment sequence. The results showed that mean increase in fat absorption as measured by Coefficient of Fat Absorption (CFA %) with Ultrase® treatment compared to Placebo treatment was an improvement of + 34.7 (SD ± 25) points on the CFA %, a clinically and highly statistically significant result ($p < 0.0001$).[2] This magnitude of improvement in CFA % is similar to the results seen in other PEPs. Subgroup analysis showed that those patients who had a lower capacity for fat absorption on Placebo had a greater improvement with Ultrase® treatment, consistent with the theory that the more severely affected patients have a greater capacity to respond to treatment. This study supports the clinical effectiveness of the TbMP of Ultrase® MT.

The two supporting studies for efficacy were Studies 96-01 and 96-02, in which an older formulation of Ultrase® (coated with Eudragit®) MT 20 and MT 12 capsules, respectively, were used. This formulation is not to be marketed, and since the *in vivo* bioactivity/bioavailability

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1 U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl htm> April 2006.
2 This delta value was the mean of the individual treatment differences in the 24 patients who completed both treatment periods and who had evaluable stool testing results for both periods.

testing failed to establish comparability between this older formulation and the to-be-marketed formulation, these study results are used as supportive evidence of efficacy and safety only. Similar to Study UMT20CF05-01, Studies 96-01 (N= 31) and 96-02 (N=26) were multi-center, randomized, double-blind, placebo-controlled, crossover-studies designed to evaluate the safety and efficacy of Ultrase® MT in the treatment of steatorrhea in CF patients older than seven years of age, with a history of EPI. Patients were randomized 1:1. One group underwent one-week of treatment with Ultrase® MT capsules, followed by one-week treatment with Placebo; and the other group, vice versa in their treatment sequence. The results showed that mean increase in fat absorption as measured by Coefficient of Fat Absorption (CFA %) with Ultrase® treatment compared to Placebo treatment was an improvement of + 29 points on the CFA %, a clinically and highly statistically significant result ($p = 0.0001$) for Study 96-01, and similarly, + 33 points on the CFA % ($p = 0.0002$) for Study 96-02. This magnitude of CFA % improvement on Ultrase® MT 20 and 12 using the Eudragit® formulation provides supportive evidence for efficacy, and is within the expected range with that of Ultrase® MT HP-55 (the TbMP), as well as other PEPs in the same drug class.

Approximately ninety patients in the three studies' safety population (Studies UMT20CF05-01, 96-01, and 96-02) had a mean age ranging from 16.5 (6.5 SD) to 19.6 years (6.6 SD), with an overall range of 7 to 37 years. This pooled safety population was comprised approximately of Caucasian (92%), Black (5%), Hispanic (2%), and Black/Caucasian (1%) patients. There were no deaths. Serious Adverse Events (SAEs) and Adverse Events (AEs) that caused dropouts, mostly respiratory and gastrointestinal events, were likely related to the underlying disease of CF. Common adverse events were predominantly gastrointestinal events (e.g., abdominal pain, flatulence, nausea, fecal fat increased, abnormal laboratory test), and all of these had a higher incidence in patients during the Placebo phase, likely reflecting not a "safety concern" per se, but rather, a lack of efficacy from absent PEP treatment. Given that dosing was within the established guideline, and the study population was small and the study treatment was very short, as expected, there were no cases of fibrosing colonopathy, a rare but serious condition thought to be related to excessively high dosing of PEPs. Additional supporting evidence of a favorable safety profile came from post marketing safety surveillance, as well as literature review. In sum, data on patients from the three short-term the placebo-controlled safety studies in conjunction with post-marketing safety data and published reports provided sufficient evidence for the safety of the product.

In the opinion of this Reviewer the risk benefit analysis for Ultrase® MT is favorable, and from a clinical standpoint Ultrase® MT could be approved to treat CF patients with EPI older than seven years of age. Furthermore, efficacy and safety could be extrapolated to patients who suffer EPI from other causes (for example, chronic pancreatitis due to alcoholism or pancreatectomy) given that there is a general consensus that EPI due to any cause has similar clinical findings and should respond similarly to this drug.

1.3 Recommendations for Postmarketing Risk Management Activities

None is warranted at this time.

1.4 Recommendations for other Post Marketing Activities/Phase 4 Commitments

None is warranted at this time.

2 Introduction and Regulatory Background

2.1 Disease Background and Product Information

Exocrine pancreatic insufficiency (EPI) is the inability to properly digest and absorb fats, proteins, and carbohydrates due to a lack of digestive enzymes produced by the pancreas. Pancreatic enzyme supplements improve digestion by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances, and starch into dextrins and short chain sugars. These enzymes (lipase, proteases, and amylase), break down fats (lipase), proteins (proteases), and carbohydrates (amylase), into elementary units of small size that can traverse the intestinal mucosa, incorporate into the blood stream to work as sources of energy and building blocks of cells. EPI typically results from chronic loss of pancreatic tissue due to a number of underlying conditions. In children, cystic fibrosis (CF) is the most common cause of EPI. In adults, alcoholism or idiopathic pancreatitis-related chronic pancreatitis (CP) is the most common. A number of other less common causes are possible, such as pancreatic cancer, surgical removal of the pancreas, trauma to the pancreas, etc. Whatever the cause, the loss of digestive enzymes leads to mal-digestion and mal-absorption of nutrients. Symptoms can range from mild to severe, and can include a distended abdomen, flatulence, and frequent, bulky, greasy, foul-smelling stools. EPI can significantly impact on morbidity and mortality: retarded growth and development, impaired immune response, infections, and bleeding tendencies, etc.

Treatment of EPI includes treatment of the underlying condition to prevent further pancreatic damage; vitamin supplementation; diet modification that uses a low-fat, high-protein and high-calorie diet to maintain adequate nutrition and appropriate weight; and pancreatic enzyme replacement, which is prescribed to be taken in adequate amount with each meal and snack. Although carbohydrate and protein mal-absorption/digestion can be easily abolished using this strategy, fat mal-absorption/digestion (steatorrhea) is rarely abolished.[3] Still, due to advances in treatment strategies that include the use of PEPs, most CF patients born in the 1990's can expect to live for 40 years or more, whereas before the mid-1960's, the median age of death of children with CF was two years. The safety and efficacy of PEPs has been well established in clinical practice.

This New Drug Application (NDA) is for the New Molecular Entity (NME) pancrelipase. The proposed trade name is Ultrase® MT. Ultrase® is purified exocrine pancreatic enzymes extracted from the hog/porcine pancreas. Ultrase® mainly consists of the enzymes lipase, proteases, and amylase, and is intended to treat EPI due to CF and CP, and other related conditions. The drug substance (DS) (pancrelipase) is manufactured by (b) (4) (b) (4) and the drug product (DP) is manufactured by Eurand S.p.A. The

3 Pongprasobchai, S. & DiMagno, E.P. (2005). Treatment of Exocrine Pancreatic Insufficiency. In C. Forsmark (Ed.) *Pancreatitis and its Complications.* (pp. 295-312). Totowa, New Jersey: Humana Press.

Applicant/Sponsor is Axcan Scandipharm, Inc. (Axcan), who is also responsible for the final packaging and product release.

The drug is oral capsules. Each capsule contains enteric-coated minitablets. The minitablets are composed of pancrelipase and compendial excipients in a compressed form. The capsules are to be taken orally with each meal or snack. The proposed starting dose is 500 to 1,000 lipase USP units (units)/kg/meal, with titration to a maximum of <2,500 units/kg/meal or <4,000 units/g fat/day. The total daily dose is not to exceed 10,000 units/kg/day (accounting for 3 meals and 2 snacks, with the snack dose being half of the meal dose). These dosing recommendations follow the guidelines of the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA in order to optimize therapy while minimizing the risk of fibrosing colonopathy. For a 70 kg man, this amounts to a starting dose of 35,000 to 70,000 units/meal, with titration up to 175,000 units/meal. For an average two year child who weighs 13 kg, this amounts a starting dose of 6,500 to 13,000 units/meal, with a titration up to 32,500 units/meal.

The inactive ingredients are: gelatin, hydrogenated castor oil, colloidal silicon dioxide, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, hydroxypropyl methylcellulose phthalate (HP55), talc, triethyl citrate, iron oxides and titanium dioxide.

Three capsule strengths are available (see Table 1, copied electronically from the Sponsor's submission).

Table 1 Composition of pancrelipase in Ultrase® MT capsules

Product	Lipase (USP Units)	Protease (USP Units)	Amylase (USP Units)
ULTRASE® MT12 Capsules (13, 800 U/USPL)	(b) (4)		
ULTRASE® MT18 Capsules (20, 700 U/USPL)			
ULTRASE® MT20 Capsules (23, 000 U/USPL)			

The TbMP Ultrase® MT Capsules contain a hydroxypropyl methylcellulose phthalate[4] (HP-55) coating. The purported advantage of this acid-resistant coating (which dissolves only at a relatively basic environment of pH ≥ 5.5) is that it can prevent inactivation of the pancreatic enzymes by gastric acid in the stomach, thereby delivering the drug in a predictable manner with high levels of biologically active enzyme reaching the duodenum at the intended site of biologic and therapeutic activity. This formulation was used in the pivotal study (Study UMT20CF05-01). The remaining clinical studies used an older formulation, Ultrase® MT capsules coated with the water-based Eudragit® LD 30, a formulation not intended for marketing.

4 Hypromellose phthalate (official USP nomenclature)

The Sponsor proposed the following indication:

[redacted] (b) (4)

The Sponsor proposed to state in the label that [redacted] (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Ultrase® MT is currently marketed in the US, and has been available on the US market since 1991. Given this long use record, it is appropriate that only limited, short-term studies are required for the submission of this NDA.

Numerous pancreatic enzyme products (PEPs) are currently available on the US market (see Table 2, which lists some of the available PEPs in the US), but none has an approved NDA. For a discussion on the regulatory status of these products see the following sections: Section 2.3 Availability of Proposed Active Ingredients in the United States, and Section 2.4 Important Issues with Consideration to Related Drugs.

Table 2 Selected pancreatic enzyme products that are available for clinical use in the US

Manufacturer	Brand Name
Solvay Pharma	Creon®
Axcan Scandipharm	Ultrase MT®
Axcan Scandipharm	Viokase®
Digestive Care	Digestizyme® (Pancrecarb)
Eurand SpA	Zentase™
McNeil Pediatrics	Pancrease MT®
Altus	TheraCLEC-Total™
Ethex	Multiple brands

2.3 Availability of Proposed Active Ingredient in the United States

Pancreatic enzyme products (PEPs) have been available in the US since before the enactment of the Federal Food, Drug, and Cosmetic Act (The Act) of 1938; and, the majority has also been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962). Thus, the majority has never undergone formal evaluation either under Investigational New Drug (IND) applications or New Drug Applications (NDAs). The only product that has received an FDA NDA approval is Cotazym® (sponsored by Organon, Inc), but Cotazym® is not currently marketed. Therefore, no PEP currently on the market in the US holds an approved NDA.

PEPs that are on the market are available in a variety of ways, as non-prescription nutritional supplements, over-the-counter medications (OTC), or by prescription. Various dosage forms of pancreatic enzyme drug products are available as uncoated tablets, powders, capsules, enteric-

coated tablets, and encapsulated enteric-coated micro-spheres. These formulations are not considered to be clinically interchangeable. As part of an OTC drug review program in the 1990's, FDA evaluated the safety and effectiveness of PEPs, and found significant variation in bioavailability among the various dosage forms and among products from different manufacturers of the same dosage form. These variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (e.g., from lot to lot, and even within lots) were thought to have a critical effect on safety and efficacy. Based on this, FDA concluded that formal FDA review and pre-clearance of each product to standardize enzyme bioactivity would be needed. FDA also determined that since continuous physician monitoring of patients is necessary for the safe and effective use of PEPs, these products should be available by prescription only, hence the products should be approved through the new drug approval (NDA) process to standardize enzyme activity. FDA announced these requirements in the Federal Register on 28 April 2004 (herein referred to as the 2004 FR Notice). And, a Guidance document published by FDA for submitting NDAs for PEPs was published in the Federal Register of 14 April 2006, 71 FR 19524 (herein referred to as the Guidance).[5]

The 2004 FR notice advised the public that FDA intended to exercise its enforcement discretion until 28 April 2008, because the Agency considered PEPs medically necessary, and intended that PEPs would remain available on the market during the period necessary for manufacturers to conduct the required studies, prepare applications, and have the applications approved. In response to the 2004 FR Notice, however, a number of manufacturers indicated that they need an extension of time beyond the original deadline of 28 April 2008 to obtain approved applications. The manufacturers contend that additional time is needed because of numerous problems encountered during the drug development process, predominately manufacturing issues, and difficulty conducting all of the required studies needed for IND and NDA filling and approval. The Agency considered these requests, and extended the deadline. In an FR Notice dated 26 October 2007, FDA extended the period during which it intends to exercise its enforcement discretion until 28 April 2010. However, this extension applies only to any manufacturer of PEPs marketed on or before publication of the 2004 FR notice, and if the manufacturer has an active IND for its PEPs on or before 28 April 2008, has submitted an NDA on or before 28 April 2009, and is pursuing approval of its application with due diligence. For a complete listing of FR notices pertaining to the regulatory history of PEPs, see Appendix 1.

2.4 Important Safety Issues with Consideration to Related Drugs

Porcine-derived PEPs have been in clinical use in a global market for over 70 years, and as such, there is extensive clinical experience with these products in humans. The long-term safety experience shows that the PEPs are safe in the context of demonstrated clinical benefits of PEP treatment. In consideration of this long and extensive safety experience, the Guidance states that only short-term safety evaluation is required. The Guidance also specifies that since PEPs are locally acting agents in the gastrointestinal tract and are not absorbed systemically into the blood stream, safety monitoring should focus on gastrointestinal adverse events such as manifestations

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

of steatorrhea, complaints of bloating, flatus, abdominal pain, loose and frequent stools, overt diarrhea, and blood in the stool, and other known adverse events associated with PEPs administration, such as uric acid elevations.

A noteworthy concern of the PEPs is fibrosing colonopathy, a rare but serious condition, whose etiology has not been elucidated. It has been suspected that high or inappropriate dosing of PEPs may play a role, although theories about the role of the excipients (including Eudragit®) have also been discussed. In an effort to minimize the development of fibrosing colonopathy that has been assumed to be related to high doses of PEPs, the FDA, in conjunction with the Cystic Fibrosis Foundation (CFF), recommends a starting dose of 500 to 1,000 lipase units/kg/meal with titration to less than 2,500 units/kg/meal or less than 4,000 lipase units/g fat consumed/day.[6,7] Doses in excess of 2,500 units/kg/meal should be used with caution and only if their benefit is documented by a three-day fecal fat test. Doses in excess of 6,000 units/kg/meal have been associated with fibrosing colonopathy. This dosing recommendation, applicable to any formulation, was made on the basis of concern over dose-related colonic strictures in CF patients, and the likelihood that maximal efficacy is achieved at the recommended ceiling dose of 2,500 units/kg/meal.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

IND 41,387 was received on 24 December 1992. Discussion of "refuse-to-file" for Ultrase® NDA 20,480 was held on 31 October 1994, whereby the Division recommended that the Sponsor conduct fat absorption studies in CF patients in two adequate and well-controlled studies, one using a higher strength of Ultrase®, and the second, a lower strength. Subsequently, Studies 96-01 (Ultrase® MT20) and 96-02 (Ultrase® MT12) were conducted under IND 41,387.

The Sponsor submitted a separate NDA (NDA 22,222) on 31 July 2007, but due to deficiencies in the Drug Master File (DMF), the Sponsor was notified that the application was not reviewable. The Sponsor requested a rolling submission, which was granted with priority review status. The PDUFA goal date was extended from 1 April 2008 to 1 July 2008 due to a major amendment that was received on 12 March 2008.

Points for discussion during the pre-submission regulatory activities included the following:

- Clinical trials carried out with the Eudragit® formulation (the older formulation) can be applied to the drug product made with the HP-55 coating (the to-be-marketed formulation) only if both *in vitro* dissolution profile and *in vivo* bioavailability profile show comparability.
- For young pediatric patients, the Sponsor should develop an age-appropriate formulation with lipase content low enough to allow for flexibility for recommended weight based dosing.

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6 FitzSimmons, SC, GA Burkhart, D Borowitz et al. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. New England Journal of Medicine. 1997; 336:1283-1289
7 Borowitz, D, RD Baker, and V Stallings, Consensus report on nutrition for pediatric patients with cystic fibrosis. Journal of Pediatric Gastroenterology and Nutrition. 2002;35:246-259

- The Sponsor may request a pediatric deferral, (b) (4)

2.6 Other Relevant Background Information

The Agency has determined that there is an existing body of evidence that shows that the PEPs have clinical benefit for patients with CF and CP (69 FR 23410), and that safety and efficacy have already been established by consensus in the literature and the international medical community. Therefore, the requirement for a New Drug Approval (NDA) is less extensive and rigorous than that for a drug with a lesser clinical track record. In the Guidance document for submitting NDAs of PEPs, the Agency explained the type and amount of evidence that is required,[8] including the following discussion points, which could apply to this NDA. The duration of the entire pivotal trial could be days to two to three weeks, and the total number of patients in the study could be between 10 and 25, depending on the design chosen. One adequate and well-controlled clinical investigation and confirmatory evidence may be appropriate. A cross-over study in which each patient in the study is treated with the intended product and a control is an acceptable study design; demonstration that administration of the PEP to patients with EPI causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection, a pharmacodynamic endpoint, is an acceptable clinical efficacy endpoint. Because CF is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with CF. Safety variables should include symptoms and signs of malabsorption, such as manifestations of steatorrhea, complaints of bloating, flatus, abdominal pain, loose and frequent stools, overt diarrhea, and blood in the stool. The safety issues of elevation in uric acid and fibrosing colonopathy should be addressed. This Reviewer finds that in the present NDA for Ultrase® MT all of these stipulations have been met.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This Reviewer found that the overall submission quality to be acceptable, including responses by the Sponsor to FDA's Information Request letters.

The Division requested two site inspections for the pivotal study to be conducted by the Division of Scientific Investigation (DSI): Site 02 (Dr. Theodore Liou, of University of Utah School of Medicine), and Site 03 (Dr. Steven Strausbaugh, of Rainbow Babies and Children's Hospital in Cleveland, OH).

Site 02 had the highest enrollment (N=7) in this small pivotal study (N=36), and the highest incidence of "major protocol violations" (four incidents). Inspection by FDA DSI Inspector Khairy Malek, M.D. found that Site 02 had "many protocol violations… Four subjects were allowed in the study before confirmatory testing of pancreatic insufficiency by way of fecal

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

elastase testing… At the beginning of the study, the dietician was sick and the Principle Investigator allowed the study to proceed before getting another dietician. This resulted in poor dietary control and deviation from the protocol, which required 2 g of fat/kg of body weight ± 15% for almost all the subjects. In addition three subjects…had poor dietary compliance during various Stabilization and Treatment Periods." But despite of these findings, the conclusion reached by the inspector was that these violations would not affect the validity of the data or markedly affect the calculation of the coefficient of fat absorption, which is the primary efficacy parameter, and that the data from this site can be used in support of the NDA. A letter was sent to Dr. Liou by FDA, stating that he did not "adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protections of human subjects, specifically that he did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60], and that he should make appropriate corrections in his procedures to assure that the findings noted are not repeated in any ongoing or future studies."

Site 03 (Dr. Strausbaugh) had the second highest enrollment (N=6), and had the most number of patients (N=2) who did not complete the study that was not due to a screening failure: one discontinuation was due to a major protocol deviation, and the other was due to a Serious Adverse Event (SAE). The inspection revealed "minor protocol violation: two subjects were enrolled before the results of the fecal elastase tests were received. The results were found later to be within the protocol requirement. The data from this site can be used in support of the NDA."

The overall assessment by FDA's DSI inspector was that the violations described for either site will not affect the validity or reliability of the data, and that the data from the two inspected sites can be used in support of the NDA.

Two Axcan-sponsored audits were conducted (Dr. Strausbaugh, site #03; Dr. Ahrens, site #05). The Sponsor submitted the audit certificates, which state that a qualified GCP auditor has performed an audit at each site and that both sites successfully passed the audit.

3.2 Compliance with Good Clinical Practices

The Sponsor states that Study UMT20CF05-01 (the pivotal clinical study using the TbMP) and Studies 96-01 and 96-02 (the supportive studies) were conducted in compliance with and monitored according to Good Clinical Practices (GCP).

For the pivotal study, the Cystic Fibrosis Foundation—Therapeutic Development Network (CFF-TDN) provided extensive support in the design, implementation, and analysis of the study. The Cystic Fibrosis Foundation also functioned as the study's Data and Safety Monitoring Board (DSMB), and Data Monitoring Committee (DMC).

3.3 Financial Disclosures

Pursuant to 21 CFR 54 and 21 CFR 314.50(k), financial disclosure information has been obtained from all investigators participating in Studies UMT20CP05-01 (the bioavailability

study) and UMT20CF05-01 (the pivotal clinical study using the TbMP): no investigator had any financial interest to disclose.

Study 96-01 was initiated on 1 April 1997 and completed in August 1998. Study 96-02 was initiated on 4 August 1997 and completed in August of 1999. These trials were sponsored by Scandipharm Inc., which was a privately-held company at the time the trials were conducted. Scandipharm Inc. was subsequently purchased by Axcan on 2 August 1999. Because these trials were initiated prior to the effective date of the final rule on financial disclosure requirements, no financial disclosure information was collected from the investigators at the time the trials were initiated. However, as per the FDA Guidance Document "Financial Disclosure by Clinical Investigators," Axcan has established that to the best of its knowledge there were no financial arrangements or interests in these studies of concern to FDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

At the time of this writing, the CMC reviews and recommendations are pending, although issues have been identified as deficiencies that will lead to an Approvable (AE) action. Please see reviews by FDA reviewers Wei Guo, Ph.D. (CMC) and Ennan Guan, Ph.D. (virology) for details.

4.2 Clinical Microbiology

Ultrase® MT is a dry solid oral dosage form of pancreatic enzymes derived from porcine pancreas. The drug substance (DS), pancrelipase, is not sterile. The drug product (DP), Ultrase® MT, consists of solid non-sterile capsules with a core of minitablets composed of pancrelipase and compendial excipients. The original submission proposed microbial limits of no more than (b) (4) CFU/g for total plate count, and an absence of *E. coli and Salmonella* species. In a January 2007, in response to an FDA Information Request letter, the Sponsor changed the microbial limits specifications to no more than (b) (4) CFU/g total plate count, no more than (b) (4) CFU/g yeast and mold, and an absence of *E. coli and Salmonella* species. The (b) (4) For additional details, please see Microbiology Review by FDA microbiology reviewer Stephen Langille, Ph.D. Approval is recommended.

4.3 Preclinical Pharmacology/Toxicology

Preclinical pharmacology and toxicity studies of the active ingredient (pancrelipase) were not needed, given the long history of its use in patients with EPI. The submitted toxicology information was mostly related to the excipients and phthalic acid (a major impurity) in Ultrase® MT Capsule. The need for excipient toxicity information arose from the fact that the expected daily ingestion of PEPs is a large number of capsules, and therefore, the quantity of excipients ingested is substantial. The Sponsor provided toxicity and regulatory information about the

following excipients: croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP 55), triethyl citrate, talc, iron oxide, and gelatin, i.e., for excipients where the daily intake could exceed the maximum daily oral dose among all FDA-approved drug products, as determined from the maximum daily dose of Ultrase® and information from the FDA Inactive Ingredients Database. In his review, FDA pharmacology-toxicology reviewer David Joseph, Ph.D. concluded that the estimated maximum dose for these excipients and phthalic acid were not considered to be a safety concern. Approval is recommended.

A special toxicology study of a porcine PEP was also submitted, and the objective of the study was to investigate the underlying mechanism of fibrosing colonopathy, a condition that has occurred in children with CF apparently after treatment with high levels of pancreatic enzymes. Rats were treated with oleic acid and/or reserpine to produce a chemically-induced, increased intestinal permeability, a pathological condition that is characteristic of CF-related EPI. High doses of Ultrase® were then administered. The results suggest that high dose levels of pancreatic enzymes can produce injury in the small intestine under conditions of increased intestinal permeability. However, it should be emphasized that the intestinal lesions in this study differ from those of fibrosing colonopathy, which is characterized by submucosal fibrosis of the colon and rectum, and colonic strictures. The lesions in rats were limited to the ileum and jejunum in the form of muscle necrosis. While suggestive, this study does not fully characterize the relationship between high-dose PEP and fibrosing colonopathy lesions in humans.

4.4 Clinical Pharmacology

The purpose of the clinical pharmacology review was two fold: 1) to test equivalence by way of establishing comparable bioactivity and/or bioavailability of the active ingredient at the site of action between the two product formulations (Ultrase® MT coated with HP 55 and Ultrase® MT coated with Eudragit®); 2) to test the *in vitro* stability of the contents of the Ultrase® MT HP-55 capsules to establish that Ultrase® capsule content may be sprinkled on food to allow patients who cannot swallow capsules to take the medication as sprinkled powder mixed into foods.

The *in vivo* bioactivity/bioavailability study (Study UMT20CP05-01) could not establish that the two formulations were equivalent. The *in vitro* stability Study (No. RE-071211-01) did establish product stability in conditions that simulate real-world use. Therefore, the recommendations are 1) since the bridging study could not establish formulation equivalence, final approvability of the TbMP will need to be based on clinical findings conducted in patients who received the TbMP; and 2) the TbMP may be sprinkled on food for patients who cannot swallow capsules.

In a joint meeting between the Division of Clinical Pharmacology 3 and the Division of Gastroenterology Products, consensus was reached that based on the experiences gathered in reviewing the PEP NDAs submitted so far (for Creon®, Zentase®, and Ultrase®) regarding the *in vivo* bioactivity/bioavailability intubation studies. FDA now recognizes that there are many challenges in the study design, study conduct, and assay methodology that limit interpretation of the results of these studies, and in view of the timeline imposed by the Agency on sponsors for submitting NDAs for PEPs, it is decided that intubation studies of bioactivity/bioequivalent for PEPs will no longer be required for future PEP NDA submissions, though a formal public statement has not be released. And, from this point forward when demonstrating bioequivalence

between formulations is necessary, the Sponsor will be encouraged to conduct clinical studies rather than relying upon bridging bioactivity/bioavailability studies.

4.4.1 Mechanism of Action

Please see Section 2.1 Disease Background and Product Information.

4.4.2 Pharmacodynamics

Since lipase, amylase, and proteases act locally in the gastrointestinal tract and are not systemically absorbed, pharmacodynamic studies are not applicable and have not been conducted.

4.4.3 Pharmacokinetics

Since lipase, amylase, and proteases act locally in the gastrointestinal tract and are not systemically absorbed, pharmacokinetic studies are not applicable and have not been conducted.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The clinical studies submitted are summarized in Table 3:

Table 3 List of clinical studies submitted by the Sponsor in support of NDA 22-222

Study	Design	Patient Population	Formulation Used
UMT20CF05-01* *pivotal study (Final clinical study report submitted) Study completed: 2007	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over study of the safety and efficacy of Ultrase® MT20 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 8-37 years Mean age: 20 years N=31	To-be-marketed formulation (HP-55 coating)
96-01 (Final clinical study report submitted) Study completed: 1998	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of the safety and efficacy of Ultrase® MT20 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 7-36 N=31	Older formulation (Eudragit® coating)—not intended for marketing
96-02 (Final clinical study report submitted) Study completed: 1998	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of the safety and efficacy of Ultrase® MT12 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 8-36 N=26	Older formulation (Eudragit® coating)—not intended for marketing
Study 01 (Final study report submitted as legacy report—no SAS datasets) Study reported: 1994	Open-label study of safety and efficacy comparing Ultrase® (MT12, 20, 24) vs. patient's one year history on their usual medication. Two weeks on Ultrase® treatment phase; one year of historical phase	CF patients with EPI and steatorrhea ≥ seven years old Age range 1-40 N=171	Older formulation (Eudragit® coating)—not intended for marketing
Study 02 (Abbreviated report submitted as legacy report—no SAS datasets) Study reported: 1994	Open-label study of safety and efficacy comparing Ultrase® (MT12, 20, 24) vs. patient's usual medication. Three weeks on patient's usual medication, and three weeks on Ultrase®	CF patients with EPI and steatorrhea from 9 months to 31 years Age range: 9 months-31 years N=25	Older formulation (Eudragit® coating)—not intended for marketing
UMT20CP05-01 Bioavailability study **(Final clinical report submitted)** **Study completed: 2006**	Single-center, randomized, open-labeled, cross-over study of lipase *in situ* availability in subjects with chronic pancreatitis using two enteric-coated formulations of Ultrase® MT (Eudragit® LD30 and HP55 coating).	Age range: 19-75 Median age: 56 N=13	To-be-marketed formulation (HP-55 coating) and older formulation (Eudragit® coating)—not intended for marketing

5.2 Review Strategy

The pivotal clinical study was Study UMT20CF05-01, the sole clinical study that used TbMP. Since the pivotal study was the only study that was conducted with TbMP, the entire clinical review and assessment of short-term efficacy rests on this study. A single, short-term efficacy (and safety) study is consistent with the Guidance recommendations, and is acceptable as a 505(b) (2) application.

The older two clinical studies (Studies 96-01 and 96-02) provide supportive evidence for efficacy and safety. These studies used an older Ultrase® MT formulation that contained the Eudragit® coating, a formulation not intended for marketing. Their efficacy findings are briefly summarized in this review (see Section 6.1.19 Additional Efficacy Issues/Analyses).

Together, Studies UMT20CF05-01, and Studies 96-01 and 96-02 provided data for an integrated safety analysis.

The two oldest studies (Studies 01 and 02) were submitted as legacy reports (with Study 02 submitted as a 12-page abbreviated report) in a format that did not permit review, and therefore, this Reviewer did not rely upon these results to support the claims of safety and efficacy.

The clinical bioavailability study, Study UMT20CP05-01 was reviewed for short-term safety data only in this clinical review. The results on bioavailability were reviewed by the Clinical Pharmacology Reviewer, Tien-Mien Chen, Ph.D. (See Section 4.4 Clinical Pharmacology).

5.3 Discussion of Individual Studies

This submission contains a single study (pivotal trial) that is used to support TbMP. This pivotal study (Study UMT20CF05-01) will be reviewed in depth in Section 6 Review of Efficacy. Supportive evidence for efficacy from Studies 96-01 and 96-02 will be reviewed in Section 6.1.10 Additional Efficacy Issues/Analyses. An integrated safety analysis of all three studies will be reviewed in Section 7 Review of Safety.

6 Review of Efficacy

6.1 Indication

The Sponsor proposed that Ultrase® receive the following indication:

“ (b) (4)

Since this application is recommended to receive an Approvable (AE) action, specific wording for the indication statement was not negotiated during this review cycle. In the opinion of this

Reviewer, the following indication statement would more accurately reflect the results of the clinical data:

"Ultrase® is a pancreatic enzyme replacement therapy indicated for the treatment of steatorrhea in patients, seven years or older, with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions."

6.1.1 Methods

The pivotal study (study UMT20CF05-01) employed a cross-over design with relatively brief periods of treatment exposure of one week per treatment assignment (Ultrase® MT or Placebo). The cross-over design assumed that the condition being assessed is stable (limited drift over time), and that the treatment being assessed does not carry its therapeutic or adverse effects across the periods (carry-over effect). It also required that one period is not preferred over another on a systematic basis (period effect) and that one treatment sequence is not preferred over the other (sequence effect). The cross-over design is one of the study designs identified in the Guidance document provided by the FDA for the preparation and submission of an NDA for PEPs (April 2006; Section VI, E, 3). As identified in that Guidance, the strength of the cross-over design lies in its use of each patient as his/her own control and the use of a paired analysis. This statistical approach potentially decreases the effects of inter-patient variability, which otherwise might obscure true treatment effects. In general, fewer patients are needed to perform a cross-over study than a parallel study. One of the key elements required to ensure the validity of the cross-over study design is to ensure that the patients re-establish their Baseline between the treatment periods, which in the opinion of this Reviewer, was successfully accomplished by the design of the study.

Because the primary efficacy endpoint required precise assessment of fat and protein absorption from the marker-to-marker stool collection, it was not possible to provide for "escape" or "rescue" medication for steatorrhea or for other signs or symptoms as it might interfere with the results of the fat and protein absorption analyses. For this reason, it was important that the study treatment periods were designed to be as short as possible. Also, while these patients were established at Baseline as being 'stable' with respect to their clinical condition and optimal treatment, there was no guarantee that some changes might occur in a given patient during the study, a further reason for minimizing the study treatment period duration.

The Cystic Fibrosis Foundation - Therapeutics Development Network Coordinating Center (CFTDN) provided support in implementation and execution of the study, including participation in the discussion of the study design. This Reviewer agrees with the Sponsor that the study design was acceptable for achieving its study endpoint goals and reducing patient risks to a minimum.

The pivotal study and its efficacy results will be described next. All of the information in the Efficacy section of this review, with the exception of additional analyses in Section 6.1.10 Additional Efficacy Issues/Analyses (which describes the study designs and results of Studies 96-01 and 96-01) is limited to the pivotal study, given that it is the only study in the clinical development program that was conducted in TbMP.

6.1.1.1 Title of the Pivotal Study (Study UMT20CF05-01)

Study UMT20CF05-01 is titled: "A Multicenter, Randomized, Double-Blind, Cross-over Study to Compare the Safety and Efficacy of Ultrase® MT20 to Placebo for the Correction of Steatorrhea in Patients with Cystic Fibrosis (CF)." This is the pivotal study of the Ultrase® MT clinical development program, and it is the only study that used the to-be-marketed (TBM) formulation (Ultrase® MT capsules coated with HP-55).

6.1.1.2 Study Design

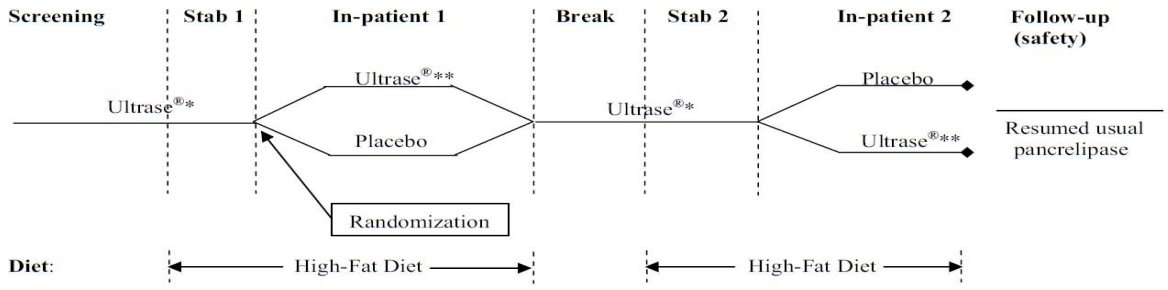
This was a multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of 31 (Intent-to-Treat) patients that evaluated the efficacy, safety and tolerability of Ultrase® MT20 capsules coated with HP-55. The study drug was either Ultrase® MT 20 or Placebo, and each study patient was randomized to receive either Ultrase® MT20 or Placebo during the first study treatment period, and the other treatment during the second study treatment period. Eligible patients were CF patients with EPI, seven years or older, maintained clinically stable on a PEP treatment, with adequate body mass index (BMI). Patients were not required to have a particular Baseline Coefficient of Fat Absorption (CFA %) level. The primary efficacy endpoint was the difference in the percent absorption of dietary fat (CFA %) between Ultrase® MT20 and Placebo Treatment. The secondary objective was the percent absorption of dietary nitrogen (CNA %) between Ultrase® MT20 and Placebo Treatment. Patients served as their own controls.

The total duration of this study for a given individual was from 41 to 49 days (including the follow-up visit). The first patient consented to the study on 30 November 2007, and the last patient completed the study on 25 April 2007.

The study design consisted of the following periods: Screening Period (up to 11 days) → Stabilization Period 1 (up to 4 days) → Inpatient Study Drug Treatment Period 1 (6-7 days) → Break Period (3-6 days) → Stabilization Period 2 (up to 4 days) → Inpatient Study Drug Treatment Period 2 → Safety follow up visit (7-10 days after discharge from Study Drug Treatment 2 hospitalization).

Figure 1 depicts the study design schematically (electronically copied from the Sponsor's submission):

Figure 1 Schematic of study design of the pivotal study



* Ultrase® = Commercial Ultrase® MT18 or MT20 or open-label Ultrase® MT20 from Axcan (during Screening).
Open-label Ultrase® MT20 from Axcan (during Stabilization Period and Break Period).

** Ultrase® = Double-blind study drug
Note: Stab = Stabilization

The Screening Period lasted up to 11 days and was completed on an outpatient basis. The patients met with the investigator and the study staff for an explanation of the study, to review and sign the informed consent form, and to be assessed for study eligibility. The medical and surgical histories and the concomitant medication history taken in the three months prior to study entry were recorded. A physical examination with vital signs was performed and clinical laboratory determinations were made, including the collection of a single stool sample to determine fecal elastase-1 content. During the Screening Visit, the patients met with a registered dietician for development of the high fat diet to be used in the two Stabilization Periods and two Study Drug Treatment Periods. Patients received instructions on how to fill out all necessary information about food intake, study drug intake, bowel movements and characteristics of their stools in a diary. Patients already on Ultrase® MT18 or MT20 continued with that treatment for the Screening Period. Patients on enzyme preparations other than Ultrase® MT18 or MT20 at study entry were switched to open-label Ultrase® MT20 for the Screening Period, and received dose adjustments based on clinical symptoms while taking their usual diets. This Reviewer could not find further details about how these procedures were accomplished, e.g., whether patients were switched to an estimated equivalent dose or to a standardized starting dose, or whether the doses were titrated based on defined clinical criteria that were standardized from site to site.

During the first Stabilization Period (Stabilization Period 1), which was completed on an outpatient basis, all patients received Ultrase® MT20 and started on their high fat diet (2 grams ± 15% per kilogram of body weight), recording all necessary information in the diary card, as instructed. The patients were instructed to adjust the number of capsules of Ultrase® MT20 needed to account for the higher amount of fat in their diet. Patients were managed to reach a stabilized status according to the clinician's observations and the patient's symptoms. The patients were considered stabilized if they had three or fewer bowel movements per day, or if additional Ultrase® MT 20 did not cause any further reduction in their stool frequency. A Stabilized Dose was determined by the investigator from the average number of Ultrase® MT20 capsules the patient took during the last two days of Stabilization Period 1 and according to his/her medical judgment. This Stabilized Dose was the dose of study treatment to be used in the in-patient Study Drug Treatment Periods as well as during Stabilization Period 2. A Break

Period of (3 to 6 days) was included to follow the end of Study Drug Treatment Period 1. During the Break Period, the patient was free from high fat diet and food recording, and was on open-label Ultrase® MT20 regimen at an *ad lib* dose.

Reviewer's comment:
The issue of a four-day Stabilization Period was discussed when the protocol was reviewed by the CFTDN. It was debated and agreed upon that since patients would be stable on a PEP treatment prior to the study, a four-day stabilization would be sufficient. But, a second stabilization would also be required because the patients would have a Break Period between Inpatient Study Drug Treatment Periods during which time they will return to their normal diets and ad lib Ultrase® dosing if desired. It was requested by FDA that the dose used in the second stabilization period (Stabilization Period 2) be the same as that was used in the first stabilization period (Stabilization Period 1), i.e., that the dose given during the second Stabilization Period be defined by the first Stabilization Period in order to ensure a proper cross-over design (see 27 July 2006 FDA Meeting Minutes with Axcan Scandipharm Inc).

On the first day of Study Drug Treatment Period 1, the participants were randomized to receive Ultrase® MT20 or Placebo, and then they were switched to the opposite treatment for Study Drug Treatment Period 2. During each day of both inpatient Study Drug Treatment Periods, the patients continued their high fat diet and received the study drug from the study personnel with each meal and snack. The number of capsules administered was the number of capsules (i.e., the Stabilized Dose) established during the Stabilization Period 1. A 72-hour stool test was performed for each of the Study Drug Treatment Periods. On Days 3 and 6 (or 7) of each Study Drug Treatment Periods, two 250 mg capsules of FD&C Blue No. 2 dye indicator (stool marker) were administered with breakfast, and the patients went through a "marker to marker" stool collection. The administration of the second FD&C Blue No. 2 marker was delayed on Day 7 instead of Day 6, if the transit time of the patient was delayed, e.g. the first blue marker did not appear in the stool within 36 hours of administration. When the first blue tinted stool appeared after administration of the first marker, this blue tinted stool was not saved but all stools from subsequent bowel movements were saved until the appearance of the second stool marker, which was administered on Day 6 or Day 7. This first stool containing the second marker was saved and marked the end of the stool collection. The stools collected represented a 72-hour stool sample collection. The patients were discharged after the completed stool collection and after the completion of the procedures scheduled on Day 6 or Day 7.

Patients were monitored throughout the study for the occurrence of adverse events (AEs). A follow-up contact was made seven to ten days after discharge from hospitalization of Study Drug Treatment Period 2, either by a telephone call for those patients with no abnormal findings during the study, or by a clinic visit for those who showed any abnormal findings (physical examination, vital signs, and laboratory tests) during the study.

6.1.1.3 Study Objectives

The primary objective of this study was to demonstrate the efficacy and short term safety of HP55-coated Ultrase® MT20 for the correction of steatorrhea in CF patients with a history of EPI.

6.1.1.4 Patient Population

Key Inclusion Criteria

Patients were eligible for study participation if they fulfilled the following:

- Patients must have a confirmed diagnosis of CF based on one or more clinical features consistent with the CF phenotype, and one of the following:
    1. A genotype with two identifiable mutations consistent with CF.
    2. A sweat chloride test > 60mmol/L by quantitative pilocarpine iontophoresis.
- Patients must have pancreatic insufficiency as demonstrated by a fecal elastase (FE-1 < 100 µg/g of stools in ScheBo test) and must require pancreatic enzyme supplementation.
- Patients must be 7 years of age or older.
- Patients must have an adequate nutritional status based on Body Mass Index (BMI) measurements:
    1. Patients 7 to 20 years old must have a BMI ≥ 5th percentile.
    2. Female patients >20 years old must have a BMI ≥16.
    3. Male patients >20 years old must have a BMI ≥16.5.
- Patients must be on an "optimal" (not otherwise defined by the Sponsor) clinical dose of pancreatic enzymes (Ultrase® MT 12, MT18 or MT20 or other pancreatic enzymes preparations) prior to entry in the study, and must tolerate this medication.
- Patients must be able to swallow capsules and must be able to eat a high fat diet, calculated as 2 g (± 15%) fat/kg of body weight per day.

Key Exclusion Criteria

Patients were excluded from study participation for any of the following:

- Patients who use narcotics or bowel stimulants and/or laxatives on a regular basis.
- Patients receiving enteral tube feeding and not willing to stop during the course of the study.
- Patients known to have a significant medical disease that would compromise their welfare or confound the study results including any of the following: acute pancreatitis, pulmonary infection, history of bowel resection, dysmotility disorders, chronic or severe abdominal pain, clinically significant portal hypertension, poorly controlled diabetes,
- Patients who have a condition known to increase fecal fat loss including any of the following: celiac disease, biliary cancer, biliary stricture, cholelithiasis, Crohn's disease, pancreatic cancer, radiation enteritis, tropical Sprue, Whipple's disease, lactose intolerance, pseudomembranous colitis.
- Female patients who are pregnant or lactating.

6.1.1.5 Concomitant and Prohibited Medications

Since the primary endpoint of this study is a measure of dietary fat absorption, drugs or products known to have an effect on fat absorption or to interfere with the fecal fat test were prohibited during the study, including the following: enema, barium, potassium chloride, mineral oil and castor oil, calcium carbonate, olestra, magnesium hydroxide, all fat-blocking nutritional supplements, over-the-counter enzymatic supplements, gastrointestinal motility modifiers, narcotics, erythromycin, acute use of broad-spectrum antibiotics, and all laxatives (with the exception of bisacodyl if prescribed by the investigator especially during the in-patient 72-hour stool collection period). It was not stated in the protocol that agents that could change the pH of the stomach content were specifically prohibited (e.g., H_2 antagonist, proton-pump inhibitors, sucralfate, antacid, etc).

6.1.1.6 Study Visits and Procedures

Study visits and procedures are presented in Table 4 below (copied electronically from the Sponsor's submission).

Table 4 Schedule of events

PROCEDURES	SCREENING PHASE	COMPARISON PHASE																	
		Stab*	Treatment Period 1 in days (D)							OP**	Stab*	Treatment Period 2 in Days (D)							Follow-up
	D-15 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D-10 to D-7	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	7 to 10 days after discharge
Informed Consent	X																		
Inclusion/Exclusion	X																		
Medical History and Demographics	X																		
Physical Exam and Vital Signs	X							x[4]	x[4]								x[4]	x[4]	
Clinical Laboratory Tests and Urinalysis	X							x[5]	x[5]								x[5]	x[5]	
Serum Pregnancy Test[1]	X																x[5]	x[5]	
Fecal Elastase Determination[2]	X																		
Morning Weight	X		x	x	x	x	x	x				x	x	x	x	x	x		
Concomitant Medication[3]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dietician and Study Nurse Instructions	X																		
Dispense Diary/open label Ultrase MT20	X							x[5]	x[5]										

* Stabilization Period (at home) **Out Patient Phase

[1] For Women Of Child Bearing Potential only. [2] On a random sample of stool. [3] Taken in the last 3 months. [4] Any time during the day the second marker has passed. If an AE appears between the time the physical examination is done and the blue tinted stool has passed, another physical examination is needed to assess this AE. [5] After second dye marker is passed.

Source: Appendix 16.1.1 Protocol UMT20CF05-01

PROCEDURES	SCREENING PHASE	COMPARISON PHASE																	
		Stab*	Treatment Period 1 in days (D)							OP**	Stab*	Treatment Period 2 in Days (D)							Follow-up
	D-15 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D-10 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	7 to 10 days after discharge
Ultrase Treatment (personal or newly introduced)	x																		
Stabilization on open label Ultrase MT20		x									x								
High Fat Diet		x	x	x	x	x	x	x[7]	x[7]		x	x	x	x	x	x	x[7]	x[7]	
Diary Records[6]		x	x	x	x	x	x	x			x	x	x	x	x	x	x		
Randomization/ Kit number assigned			x																
Double-blind Ultrase MT20 vs Placebo			x	x	x	x	x	x[7]	x[7]			x	x	x	x	x	x	x	
FD&C Blue No 2 dye with breakfast (stool marker)					x			x[8]	x[8]					x			x[8]	x[8]	
72-hour stool collection					x	x	x	x[9]	x[9]					x	x	x	x[9]	x[9]	
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Discharge of period treatment								x[4]	x[4]								x[4]	x[4]	
Follow up visit																			x[10]

* Stabilization Period (at home) ** Out Patient Phase
[6] Diary to include food records, capsules count, number and characteristics of stools and abdominal symptoms. Diary to be completed by patient during stabilization and by the study personnel from D1 to D6-7. [7]To stop at discharge. [8]If the first dye marker is not passed within 36 hours of administration, administer the second dye marker 96 hours after the first dye marker (Day 7). [9]Stool collection until second dye marker is passed. [10]Assessment to be performed by phone or during a visit with the investigator if judged necessary, to follow any abnormal findings during the study (physical exam, vital signs, lab tests, AE, etc.)

Source: Appendix 16.1.1 Protocol UMT20CF05-01

6.1.1.7 Randomization, Blinding, Control

Randomization was 1:1, and by central randomization, not stratified by center or any other criteria. The study was double-blind only during the two Study Drug Treatment Periods, and was achieved using identical capsules for the two treatments and identical packaging. The study was placebo-controlled. The placebo capsules used in this study had the same appearance as the Ultrase® MT20 capsule with respect to size, color and imprinting. The placebo capsules were composed of size 0 capsules (body yellow/cap grey opaque) containing uncoated Avicel® spheres (Avicel® is microcrystalline cellulose, USP). In the opinion of this Reviewer, however, blinding might not have been entirely possible, due to the likelihood of an increased incidence/severity of steatorrhea while on placebo, after patients having been stabilized to having <3 stools per day on the Stabilizing Dose during the Stabilization Period. But, given that the primary endpoint was an object measure of CFA %, this should not have affected the study results.

6.1.1.8 Study Medication Dose Selection, Dispensing, and Compliance

Pre-selection of set dose or dose ranges was not possible for this study since the daily dose to be used by a patient was determined on an individual patient basis according to their EPI signs and symptoms.

In this study, optimal Ultrase® MT20 dosages were based upon adjustment of the patient's usual pancrelipase dose, modified in response to the introduction of the high fat diet. The dose to be administered during the treatment periods was established for each patient during the first

stabilization period (Stabilization Period 1), at which time the high fat diet was initiated. The patients adjusted their dose of open-label Ultrase® MT20 to account for the increase of fat in their diet. They were medically managed to reach a "stabilized" status according to the clinician's observations and the patient's symptoms. The patients were considered "stabilized" if they had three or fewer bowel movements per day or if additional Ultrase® MT 20 did not cause any further reduction in stool frequency. The Stabilized Dose was determined by the investigator from the average number of Ultrase® MT20 capsules the patient took in the last two days of Stabilization Period 1 and according to his/her medical judgment. This Stabilized Dose was the dose of the Study Drug used in both Study Drug Treatment Periods as well as during both Stabilization Periods. The total daily number of capsules was then dispensed with each meal and snack throughout the day. The dose was not to exceed 2,500 lipase units/kg/meal or snack.

Compliance was calculated from the capsule counts reported during the double-blind Study Drug Treatment Periods. There were two compliance measurements, one for Study Drug Treatment Period 1 and one for Study Drug Treatment Period 2. There was no measurement of compliance during the Screening Phase and the Stabilization Periods.

As for the extent of exposure, the patient's last day of treatment was not taken into account in the treatment compliance calculation. These two compliance measurements were computed as follows:

$$\frac{\text{Total number of capsules taken during the treatment period*}}{\text{Number of prescribed capsules/day x treatment period extent of exposure*}} \times 100\%$$

* Excluding the last day of treatment for both Treatment Periods.

Non-compliance was defined as taking less than 80% or more than 120% of the dose established during Stabilization Period 1 (the Stabilized Dose).

6.1.1.9 Efficacy and Endpoint Measurements in the Pivotal Study

The primary outcome measures were stool CFA % and safety.

The primary efficacy parameter is the Coefficient of Fat Absorption (CFA %), defined as:

$$\frac{\text{72-hour fat intake (g)} - \text{72-hour fat excretion (g)}}{\text{72-hour fat intake (g)}} \times 100\%$$

The primary efficacy endpoint was Ultrase® MT20 Treatment CFA % minus Placebo Treatment CFA %.

The Sponsor also performed a secondary efficacy analysis on the results of Coefficient of Nitrogen Absorption (CNA %).

Other efficacy assessments included the total number of daily bowel movements, and the proportion of the characteristics of the stools (hard, formed/normal, soft, or watery) between the study treatment groups.

The intent-to-treat (ITT) population was defined as all randomized patients. The safety population was defined as all patients who received at least one dose of Pancrease® MT. The per-protocol (PP) population was defined as all patients who completed the two Study Drug Treatment Periods, and had all bowel movements appropriately collected in the two complete stool collection periods with no major protocol violations. This Reviewer also analyzed an "at-lease-one CFA %" population, consisting of patients who had at least one CFA % recording from either one of the two Study Drug Treatment Periods. For additional details, please see Section 6.1.4 Analysis of Primary Endpoints.

6.1.1.10 Safety Analysis

Safety was assessed by type and incidence of Adverse Events (AEs); discontinuation due to AEs; drug-related AEs, Serious Adverse Events (SAEs), and severe AEs; changes from Screening Visit or Baseline in physical exams, vital signs, or clinical laboratory assessments. All AEs reported during this study were "treatment emergent," i.e., they were not present prior to exposure to study medication, or they were any event already present that worsened in duration, intensity or frequency following exposure to study medication. All AEs, whether or not considered causally related to the treatment, were recorded.

Serious Adverse Events (SAEs) were monitored by Axcan Pharma Inc. throughout the trial. Monitoring of SAEs was performed with special attention on intestinal obstruction. All SAEs, regardless of relationship to study treatment, were to be reported by the investigator to Axcan Pharma Inc within 24 hours of learning of the event. This included SAEs occurring as soon as the ICF/assent form was signed by the patient (i.e. pre-treatment SAEs). SAEs that were possibly related to treatment and were assessed as being unexpected could have qualified for expedited reporting by Axcan to the regulatory authorities.

Axcan Pharma Inc. sent all SAE reports within the next working day via fax or email to the Data Monitoring Committee chair of the Data and Safety Monitoring Group and to Endpoint Research. All SAEs that occurred in the 30 days following the last dose of study drug were to be reported to Axcan Pharma Inc. The Sponsor had a legal responsibility to notify the Health Products and Food Branch (HPFB) of Canada, the FDA, the European Agency for the Evaluation of Medicinal Products (EMEA) of European Union, and all other foreign regulatory agencies about the safety of the drug.

6.1.1.11 Statistical Analysis Plan

The results from a similar, earlier, cross-over study of Ultrase M20 (Study 96-01) showed a difference of 29% between Ultrase and the Placebo treatment the primary efficacy outcome measures. The mean CFA% was 59% with placebo and 87% with Ultrase, with N=25 patients. The treatment difference was highly significant. Based on these results, the Sponsor planned to have 24 completed patients. Assuming a standard deviation of 30% between Placebo and Ultrase and a two-sided alpha of 0.05, a sample size of 24 would give a power of 80% to detect a

minimum difference of 18%. The intent-to-treat (ITT) population was defined as all randomized patients. Please see the FDA Statistical Reviewer Stella Grosser, Ph.D.'s review for further details.

6.1.1.12 Protocol Amendment

The first patient consented to the study on 30 November 2007, and the last patient completed the study on 25 April 2007. The original study protocol was issued on 4 August 2006. There was one protocol amendment (dated 8 January 2007), which was instituted midstream during the study, involving mainly administrative and personnel changes, and the following amendments: addition of CNA % as a secondary objective and enteral tube feeding as an exclusion criterion; modification/clarification of the process to establish the Stabilized Dose during Stabilization Period 1; addition of the prohibited use of erythromycin; and modification of the targeted amount of fat to eat per day. Regarding the last item, it appears to this Reviewer that the amount of daily fat to be consumed was changed midstream in the study to allow more flexibility. The revised version was, "2 grams (± 15%) per kilogram of body weight, while taking into account the patient's activity level and appetite." The provision of ± 15% modifier was probably instituted because the actual amount of fat consumed by patients was more variable than that had been originally anticipated. It is unlikely that the results of the study were significantly impacted by this amendment, however.

6.1.2 Demographics

The intent-to-treat (ITT) patient population was comprised predominantly of Caucasian patients (93.5%), the remainder being Black patients (6.5%). Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. There were more males in the study (64.5%). Since CF is a genetic disease that is autosomal recessive in nature, both males and females are equally affected. The small imbalance in the gender distribution is likely a function of the small number of patients studied. The patients were between the ages of 8 to 37 years; the mean age was 20. Since CF patients live into their third or fourth decades, this represents the median age in the expected lifespan. In the ITT population, the mean years from CF diagnosis to study Screening was 19 years (range 3-27 years). The majority of patients (60%) had been on Ultrase® MT18 or 20 prior to the study start; the rest were on Ultrase® MT12 or another PEP. Age breakdown of children, adolescents, and adults is as follows in Table 5. It is worth noting that very few children younger than 12 years were enrolled in the study, which is a significant limitation in the Sponsor's clinical development program performed to date. The Sponsor intends to conduct additional clinical studies in the pediatric patients (see Section 6.1.7 Subpopulations).

Table 5 Age categorization of the ITT population in Study UMT20CF05-01

ITT population (N=31)
2-11 year group (children): 2 patients
12-18 year group (adolescents): 13 patients
>18 year group (adults): 16 patients

Additional demographics and other Baseline characteristics of the ITT population can be found in Table 6 (electronically copied from the Sponsor's submission).

Table 6 Summary of demographics and other Baseline characteristics (ITT population)

Parameter	Statistic	Overall
Number of Patients in the ITT Population	N	31
Age at Informed Consent (years)	n	31
	Mean	19.6
	STD	6.6
Gender	n	31
Male	n (%)	20 (64.5)
Female	n (%)	11 (35.5)
Race	n	31
Caucasian	n (%)	29 (93.5)
Black	n (%)	2 (6.5)
Weight at Screening (kg)	n	31
	Mean	55.56
	STD	11.61
Alcohol Habits	n	31
No, never	n (%)	10 (32.3)
Yes	n (%)	21 (67.7)
Smoking History	n	31
Non-smoker	n (%)	30 (96.8)
Ex-smoker	n (%)	1 (3.2)
Smoker	n (%)	0
Fecal Elatase-1 (μg/g of stool)	n	31
<15	n (%)	30 (96.8)
=34	n (%)	1 (3.2)

Notes:
1. Percentages based on the total number of Safety patients with available data.
Source: Table 14.1-10

6.1.3 Patient Disposition

Thirty-six (36) patients were screened; five patients were screening failures (see Table 7 for the reasons for screening failures). The remaining 31 patients were randomized, all of whom having received at least one dose of study drug, constituting the ITT population. Five of the 31 ITT patients discontinued the study prematurely either as a result of violating the protocol, withdrawing consent, or experiencing SAEs. Twenty-eight (28) patients had at least one CFA value recorded; and, 24 patients completed both Study Drug Treatment Periods and had stool results available for each treatment periods. Nine patients had at least one major protocol violations (i.e., not compliant with the high fat diet, did not have any high-fat diet diary recording, or discarded stool during stool collection). Therefore, the per-protocol population (PP) consisted of 18 patients who were not screen failures, did not have any major protocol violations, did not withdraw consent or drop-out due to an SAE, and had at least one CFA collection. Table 7 lists the disposition of all patients as described. Table 8 lists disposition of patients by study sites.

Table 7 Disposition of patients UMT20CF05-01

Patient ID	Treatment sequence	ITT	Reason for not completing the Study	Study completed	Major protocol violation	PP
0103	Screening Failure	No	SAE (increased coughing while on Ultrase®)	No	-	No
0603	Screening Failure	No	SAE (hemoptysis while on Ultrase®)	No	-	No
1002	Screening Failure	No	Patient withdrew consent during Screening (while on Ultrase®)	No	-	No
1003	Screening Failure	No	AE (increased coughing while on Ultrase®)	No	-	No
1007	Screening Failure	No	Failed inclusion criteria (Fecal Elastase >100).	No	-	No
0102	Placebo / ULTRASE	Yes	Patient withdrew consent during Study Drug Treatment Period 2 (while on Ultrase®)	No	-	No
0301	ULTRASE/ Placebo	Yes	SAE (abdominal pain) during Study Drug Treatment Period 2 (while on Placebo)	No	-	No
0505	Placebo / ULTRASE	Yes	SAE (cough, fever) during Break Period (while on Ultrase®), coming from the Placebo period	No	-	No
0601	ULTRASE/ Placebo	Yes	AE (abdominal pain, decreased appetite, flatulence, steatorrhea) during Study Drug Treatment Period 2 (while on Placebo)	No	-	No
0304	Placebo / ULTRASE	Yes	Subject inadvertently discarded stool during stool collection during Study Drug Treatment Period 2 (while on Ultrase®)	No	(Ø stool)	No
0201	ULTRASE / Placebo	Yes		Yes	Yes (Ø fat)	No
0204	Placebo/ULTRASE®	Yes		Yes	Yes (Ø fat)	No
0205	ULTRASE/ Placebo	Yes		Yes	Yes (Ø fat)	No
0207	Placebo / ULTRASE	Yes		Yes	Yes (Ø fat)	No
1005	Placebo / ULTRASE	Yes		Yes	Yes (Ø fat)	No

0602	ULTRASE/ Placebo	Yes		Yes	Yes (? fat)	No
0604	Placebo / ULTRASE	Yes		Yes	Yes (? fat)	No
0101	Placebo / ULTRASE	Yes		Yes	No	Yes
0104	ULTRASE/ Placebo	Yes		Yes	No	Yes
0105	ULTRASE/ Placebo	Yes		Yes	No	Yes
0202	ULTRASE/ Placebo	Yes		Yes	No	Yes
0203	Placebo / ULTRASE	Yes		Yes	No	Yes
0206	Placebo / ULTRASE	Yes		Yes	No	Yes
0302	ULTRASE/ Placebo	Yes		Yes	No	Yes
0303	Placebo / ULTRASE	Yes		Yes	No	Yes
0305	Placebo / ULTRASE	Yes		Yes	No	Yes
0306	ULTRASE / Placebo	Yes		Yes	No	Yes
0501	Placebo / ULTRASE	Yes		Yes	No	Yes
0502	Placebo ULTRASE	Yes		Yes	No	Yes
0503	ULTRASE / Placebo	Yes		Yes	No	Yes
0504	ULTRASE/ Placebo	Yes		Yes	No	Yes
0701	Placebo / ULTRASE	Yes		Yes	No	Yes
0901	Placebo / ULTRASE	Yes		Yes	No	Yes
0902	ULTRASE/ Placebo	Yes		Yes	No	Yes
1001	ULTRASE / Placebo	Yes		Yes	No	Yes
1006	Placebo / ULTRASE	Yes		Yes	No	Yes

(Ø stool)—no stool sample for a Study Drug Treatment Period
(Ø fat)—did not comply with high fat diet
(? fat)—did not have sufficient fat diary recording
Shaded area: 24 patients who completed both Study Drug Treatment Periods, for whom CFA % was available for both periods

Table 8 Patient disposition by site

Investigator Site	Number of patients screened	Disposition of patients (patient's ID in parenthesis)
Dr. Gavin Graff	5	1 withdrew (0102); 1 screening failure (0103)
Dr. Theodore Liou	7	4 had a major protocol violation (0204, 0205, 0207. and 0201)
Dr. Jamshed Kanga	6	3 screening failures (1002, 1003, 1007); 1 had a major protocol violation (1005)
Dr. Kathryn Moffett	4	2 had a major protocol violation—no fat/CFA % recording (0602, 0604); 1 did not complete the study due to gastrointestinal worsening while on double-blind Placebo treatment (0601); 1 screening failure (0603)
Dr. Richard Ahrens	5	1 did not complete the study due to an SAE (0505)
Dr. Samya Nasr	1	-
Dr. Steven Straughsbaugh	6	1 did not complete the study due to an SAE (0301); 1 did not finish the study--discarded stool (0304)
Dr. Susan Millard	2	-
Total	36	24 patients completed both Study Drug Treatment Periods, for whom CFA % was available for both periods

6.1.3.1 Concomitant Medication

This Reviewer used the **CV_conmd.xpt** dataset to arrive at the following observations:

- The majority of the concomitant medications were CF related.
- The most common concomitant medications (other than PEPs) were the following: Salbutamol® (91% of patients), Dornase Alfa® (69%); Tobramycin® (64%), ADEKS® (64%), Azithromycin® (53%), Ibuprofen® (39%), Seretide® (31%), Fluticasone® (31%), and Multivitamin (28%).
- There were 19/36 patients (53%) of the safety population who were taking proton pump inhibitors or H_2 blockers during the study. Except for one patient, all had started the medication before the start of the study and the vast majority had been on a stable dose of the medication for chronic use for several years. There did not appear to be a change in the pattern of use over the course of the study.

6.1.3.2 Protocol Deviations and Violations

Protocol deviations that were considered major and that were not authorized by the Sponsor were reported in nine patients; one had Study Drug non-compliance, and eight patients (22%) were non-compliant with the required high fat diet (Table 9) (copied electronically from the Sponsor's submission). Along with these major protocol violations, this Reviewer noted that there were numerous "minor' protocol deviations, mostly relating to non-compliance of the high fat diet. In most cases, the compliance was towards taking more than the allowable amount of fat, which would have probably enhanced the likelihood of seeing a treatment effect (i.e., more fat intake, more room to improve). But, the Reviewer does not believe that these protocol violations/deviations rendered the conclusions of the study unreliable.

Table 9 Summary of major protocol violations (all screened patients) in Study UMT20CF05-01

Parameter	Statistic	Overall
Number of Screened Patients	N	36
Major Protocol Violations		
Study Drug Compliance <80% or >120%	n (%)	1 (2.8)
Non-compliance with High-Fat Diet[a]	n (%)	8 (22.2)

[a] Without any protocol deviations granted by the Sponsor.
Notes:
1. Patients could have more than one major protocol violation.
2. Non-compliance with high fat diet is defined as deviating by ±10% from the targeted amount of fat (1.7 – 2.3 g of fat per kg of body weight) on multiple occasions during the stool collection periods.
3. Percentage based on the total number of screened patients.

Source: Table 14.1-3

6.1.3.3 Measurements of Treatment Compliance

Compliance to the required treatment regimen was high and consistent in the ITT population as calculated using capsule counts. Average compliance was 98.3% (SD ± 9.2 %) for the Ultrase®

treatment period, and 97.4% (SD ± 9.2 %) for the Placebo treatment period. Compliance values tended towards a slightly higher use than required, with 76.7% of patients on Ultrase® treatment being between 100% and 120% as compared to 13.3% of patients being between 80% and 100%. A similar profile was seen with Placebo (Table 10) (copied electronically from the Sponsor's submission).

Table 10 Summary of treatment compliance (ITT population) in Study UMT20CF05-01

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Treatment Compliance (%)	n	30	30
	Mean	98.3	97.4
	STD	9.2	7.6
< 20%	n (%)	0	0
20% to 40%	n (%)	0	0
40% to 60%	n (%)	0	0
60% to 80%	n (%)	2 (6.7)	3 (10.0)
80% to 100%	n (%)	4 (13.3)	6 (20.0)
100% to 120%	n (%)	23 (76.7)	21 (70.0)
> 120%	n (%)	1 (3.3)	0

Notes:

1. Treatment compliance has been calculated as follows:

$$\frac{\text{Total number of capsules taken during the Treatment Period (excluding the last day of treatment)}}{\text{(Number of prescribed capsules/day) x (Treatment Period extent of exposure in days (excluding the last day of treatment))}}$$

2. The number of prescribed capsules/day corresponds to the number of capsules/day that has been determined to be the patient's stabilized dose at the end of Stabilization Period 1 by the investigator after discussion with the Sponsor.
3. Five patients (0103, 0603, 1002, 1003, and 1007) received open-label study medication during the study Screening Phase but did not enter the study Comparison Phase.

Source: Table 14.1-22

Table 11 (copied electronically from the Sponsor's submission) presents a summary of treatment exposure in patients who were randomized to Study Drug treatment (ITT population). On average, patients were exposed to 5.4 (±1.1) and 5.0 (±1.1) days of treatment while on Ultrase® MT20 and Placebo, respectively. The mean daily number of capsules administered was similarly comparable between the treatments with 18.2 (±6.6) and 17.9 (±6.8) capsules while on Ultrase® and Placebo, respectively.

Table 11 Summary of extent of exposure and mean total daily number of capsules taken (Study UMT20CF-05-01)

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the Safety Population Who Entered the Treatment Period	N	30	31
Extent of Exposure (days)	n	30	31
	Mean	5.4	5.0
	STD	1.1	1.1
	Median	5.5	5.0
	(Min., Max.)	(1, 7)	(0, 6)
Mean Total Daily Number of Capsules Taken	n	30	30
	Mean	18.2	17.9
	STD	6.6	6.8
	Median	18.0	18.0
	(Min., Max.)	(6, 30)	(6, 32)

Notes:
1. Extent of exposure, in days, has been calculated as follows within each study period:
   (Next to the last dose date of the concerned study period – First dose date of the concerned study period) + 1
2. Mean total daily number of capsules taken has been calculated as follows within each study period:
   Total number of capsules taken during the concerned study period (excluding the last day of treatment) / Extent of exposure
3. Five patients (0103, 0603, 1002, 1003, 1007) received open-label study medication during the study Screening Phase but did not enter the study Comparison Phase.

Source: Table 14.1-21

Reviewer's comment:

Due to the constraint of the review clock, it has not be ascertained by this Reviewer whether the dosing in terms of lipase units used by patients in the study fell into the CFF/FDA recommendations, or whether the dosing is representative of how it will be used post-approval. These issues will need to be revisited and clarified with the Sponsor at the time of labeling negotiations.

6.1.4 Analysis of Primary Endpoint(s)

Primary efficacy analysis was based on an evaluation of the percent absorption of dietary fat (CFA %).

This method is clearly identified as an appropriate assessment for the purposes of this study in the CDER guidance document, Guidance for Industry - Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (CDER 2006). The Guidance states that although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea. For example, a Sponsor could

demonstrate that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection.

The Guidance bases its recommendations on published consensus documents[9] that describe that decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development.[10] A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients, where "severely affected patients" is defined as those patients who have Baseline CFA less than 40%. In patients with a Baseline CFA greater than 40%, however, there is no accepted change in CFA that has been shown to be clinically meaningful. Patients with higher CFAs at Baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Conversely, patients with the lowest CFAs at Baseline tend to have greater increases with PEP treatment as there is more "room" to improve.

No accepted clinically meaningful increase in CFA has been determined for patients with EPI due to causes other than CF. However, as EPI due to any cause has similar clinical findings as in CF, this degree of change could reasonably be applied as meaningful in EPI due to other conditions that cause EPI, such as CP. In accordance with the Guidance, the Division accepts the use of CFA as the primary efficacy measure in the clinical studies conducted in the Ultrase® clinical development program. However, the Division expects to see that the magnitude of change in patients' CFA with PEP administration would depend upon the Baseline (or no treatment/Placebo CFA), and expect to see larger increases in CFA (approaching 30%) in patients with the lowest Baseline/Placebo CFA (e.g., <40%), and lesser increases in CFA in patients with higher Baseline/Placebo CFA (e.g., >40% to <80%).

Although the Sponsor had pre-specified that the primary efficacy variable was to be analyzed in the ITT population--which is defined as all randomized patients (N=31)--the Sponsor's efficacy analyses found in Table 12 (copied electronically from the Sponsor's submission) actually reflect the results of the 24 patients who completed both Study Drug Treatment Periods, who had stool testing completed in both study periods (See Table 7: only patients in the shaded gray area). The primary efficacy endpoint is defined as change in CFA, determined by mean CFA % measured in patients in the Ultrase® Treatment Period minus the mean CFA % measured in patients during the Placebo Treatment Period. Each patient served as his/her own control in this cross-over study.

The Sponsor's efficacy analyses are given below in Table 12 (copied electronically from the Sponsor's submission). In these 24 patients (not the ITT population), the difference in CFA % between the Ultrase® Treatment Period and the Placebo Treatment period was 35 points (SD ± 25), $p < 0.0001$, a clinically and statistically significant result. There were no apparent sequence or period effects. Dropouts were not replaced, and missing observations were not imputed. There were no apparent sequence or period effects. The FDA Statistical Reviewer (Stella Grosser, Ph.D.) noted some differences in the statistical manipulation between the Sponsor's and

9 Borowitz, DS; Grand, RJ; Durie, PR Consensus Committee (supplement A). Use of pancreatic enzyme supplement for patients with cystic fibrosis in the context of fibrosing colonopathy. 1995; J Ped 127(5): pp 681-684
10 Dodge, JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46.

her independent analyses, but the statistical conclusions reached remained the same: significant treatment effect was demonstrated with no effect of period or sequence. For more details, please see Dr. Grosser's Statistical Review.

Table 12 Summary and analysis of the coefficient of fat absorption (ITT population)

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
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	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-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.				

** Indicates statistical significance at the 0.010 level.

[a] P-values from a semi-parametric mixed model on ranked CFA% values including sequence, period, and treatment group as fixed effects, and patient ID as random effect.

Notes:

1. CFA%= Coefficient of Fat Absorption
2. CFA% has been calculated as follows (in some instances, the CFA% has been calculated over 96 hours instead of 72 hours):

$$\frac{\text{72-hour fat intake (g)} - \text{72-hour fat excretion (g)}}{\text{72-hour fat intake (g)}} \times 100\%$$

3. The fat excretion value (g/24h) transferred by the Central Lab has been multiplied by 3 before analysis in order to convert it to total fat content.
4. For each patient, Delta is the difference between CFA% Ultrase MT20 value and CFA% Placebo value.

Source: Table 14.2-1

This Reviewer performed an independent analysis of the results shown in the 24 selected patients. Table 13 lists the results of patients, ranked in the order from low to high based on their CFA % with Placebo treatment (no treatment). The mean delta CFA % was a 35 point increase (SD ± 25) with Ultrase® MT treatment, a clinically significant result.

Table 13 Δ CFA % between Ultrase® treatment and Placebo in the 24 patients who completed both Study Drug Treatment Periods and who had stool results for both periods in Study UMT20CF05-01

Patient	CFA Placebo	CFA Ultrase	Change in CFA
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
			Mean Δ CFA= 34.7 SD=25 Median 40.4

6.1.4.1 Additional Analyses of Primary Endpoint

This Reviewer performed additional clinical analyses to further verify that clinically meaningful improvement was seen with Ultrase®. Table 14 shows the ITT patients' results listed by ranking of Placebo (no treatment) CFA % values from low to high. For the purpose of this analysis, patients without both CFA % measurements for Ultrase® Treatment Period and the Placebo Treatment Periods were conservatively assigned a Δ CFA % of zero (which assumed that for these patients, there was no improvement seen in CFA % with Ultrase® treatment). It was also assumed that Δ CFA % would not be a negative number (i.e., that PEP treatment would not result in a worsening in CFA %) based on the knowledge that PEPs are known to be efficacious. This Reviewer recognizes, however, that the latter assumption may not entirely valid given that even in this study some patients were shown to have negative CFA % change with Ultrase® treatment. Nonetheless, the changes in the negative directions were relatively small, probably within the error of the test, so the assumption is likely reasonable. In any event these analyses are not meant to arrive at mathematically rigorous conclusions, but are intended to be used as sensitivity analyses to see if the results conform to a biologically/physiologically plausible hypothesis.

The results in Table 14 show that patients with the lowest Placebo CFA % had the highest gain in CFA % improvement on Ultrase® treatment, which is consistent with the presumption that patients with the lowest CFA % should have greater increases with PEP treatment as there is more "room" to improve. CFA % < 40 has been accepted in the literature as severe malabsorption. Divided into three groups (with the moderate to mild groups being arbitrarily defined by this Reviewer): Placebo CFA % < 40 % (severe); between 40 and 80% (moderate); and, > 80% (mild), the results demonstrated that the patients' CFA increase with Ultrase® treatment (Δ CFA) was +40, +30, and +2, respectively, with a median Δ CFA of +27. The results are summarized in Table 14.

Table 14 UMT20CF05-01 (Pivotal Study) Analysis of Δ CFA % in the ITT population (N=31)

SUBJECT	CFA Placebo	CFA Ultrase®	CFA DELTA
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
0304	91.79	.	0.00
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
0301	.	86.93	0.00
0601	.	.	0.00
0602	.	.	0.00
0604	.	.	0.00

Median Δ CFA= 26.9

SD= 26.4

By Placebo CFA:

Median Δ CFA in patients with Placebo CFA % <40 = 39.3
SD = 34.3

Median Δ CFA in patients with Placebo CFA % >40 and <80 = 30.3
SD = 17.6

Median ΔCFA in patient with Placebo CFA % >80 = 2.3
SD = 8.0

These data demonstrates that in patients with severe EPI (CFA % <40), treatment with Ultrase® result in clinically meaningful benefit, as demonstrated by a median increase in the CFA % of > 30%.

A similar analysis was performed for patients who at least one CFA % measurement (either in the Placebo Treatment Period or in the Ultrase® Treatment Period) (Table 15). Once again, missing values were assigned a Δ CFA % of zero. Similar results were obtained, with increase (i.e., improvement) of the median Δ CFA % during Ultrase® treatment. The Δ CFA % for this population was better than that for the ITT population (+30 vs. +27 in the ITT population), which is to be expected given that in this analysis population more patients actually had CFA % values and were not assigned a change of CFA % of zero.

Table 15 UMT20CF05-01 (Pivotal Study) analysis of Δ CFA % in the "at-least-one CFA" patient population (N=28)

SUBJECT	CFA Placebo	CFA Ultrase	CFA DELTA
0301	.	86.93	0.00
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
0304	91.79	.	0.00
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82

Median Δ CFA = 29.8

SD = 26.2

By Placebo CFA:

Median Δ CFA in patients with Placebo CFA % <40 = 56.2
SD = 25.8

Median Δ CFA in patients with Placebo CFA % >40 and <80 = 30.3
SD = 17.6

Median Δ CFA in patient with Placebo CFA % >80 = 2.3
SD = 8.0

Based on the sensitivity analyses performed in the various efficacy populations, the conclusion reached by this Reviewer is that Ultrase® MT is efficacious. The results in the moderately to severely affected groups of patients are clinically significant. The worse/lower the CFA % at Baseline (i.e., on Placebo, or no treatment), the more the increase in the CFA% was observed. The clinical implication is that patients who have the most severe form of EPI have the most to gain to Ultrase® MT treatment.

Finally, this Reviewer examined the effect of treatment sequence on whether there was a difference in the results obtained for change in CFA % depending on whether the patients were treated first with Ultrase® or Placebo in the ITT population. Once again, for patients with missing CFA values, the Δ CFA was assigned a value of zero. The median increase in CFA % in patients who were treated first with Ultrase® MT was 25.2, as compared to 28.3 in those who were treated first with Placebo. As shown in Table 16 there does not appear to be a sequence effect.

Table 16 UMT20CF05-01 (Pivotal Study) analysis of Δ CFA % based on sequence of treatment in the ITT population (N=31)

Sequence 1: Ultrase®→Placebo (N=14)

SUBJECT	CFA Placebo	CFA Ultrase®	CFA DELTA
0301	.	86.93	0.00
0601	.	.	0.00
0602	.	.	0.00
0302	17.14	92.36	75.22
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0902	40.47	83.41	42.94
0306	41.94	90.24	48.30
0504	45.7	84.21	38.51
0104	57.24	80.87	23.63
0205	78.58	89.53	10.95
0201	89.5	89.05	-0.45
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
			Median Δ CFA = 25.2 SD = 29.5

Sequence 2: Placebo→Ultrase® (N=17)

SUBJECT	CFA Placebo	CFA Ultrase	CFA DELTA
0604	.	.	0.00
0207	13.59	88.51	74.92
0206	23.06	81.91	58.85
0203	35.14	91.96	56.82
0303	40.58	87.76	47.18
0204	44.07	92.69	48.62
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0304	91.79	.	0.00
			Median Δ CFA = 28.3 SD = 24.4

An analysis by race could not be performed since too few non-Caucasian patients were enrolled in the study. This Reviewer did not find an age or gender effect in the efficacy results.

In sum, this clinical Reviewer is in agreement with the Sponsor's and FDA Statistical Reviewer's analyses that the primary efficacy endpoint was been met and that the results of this pivotal study in the TbMP of Ultrase® MT demonstrate that Ultrase® is effective in improving

fat absorption in CF patients seven years or older with steatorrhea due to EPI, and that the efficacy results are both statistically significant and clinically meaningful. The most gain in the CFA % was observed in patients with the lowest Baseline (i.e., with no treatment, or Placebo) CFA%.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy measure was the Coefficient of Nitrogen Absorption (CNA %), defined as:

> CNA% = [(72-hr protein intake (g)/6.25) – 72-hr nitrogen excretion (g) x100] ÷ (72-hr protein intake (g)/6.25)

The effects seen in the assays for CNA % were smaller than were observed with fat absorption but the direction of the effects remained the same. The CNA % was highly statistically significantly greater for the Ultrase® MT20 treatment than for the Placebo ($P < 0.0001$). The Period and Sequence effects were not statistically significant. In patients who completed both treatment periods (N=24), the difference between the treatment was +26. Table 17 summarizes the Sponsor's analysis, which was verified by FDA statistician (S. Grosser).

Table 17 Summary and analysis of the coefficient of nitrogen absorption (ITT population) (Copied electronically from the Sponsor's submission)

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
Number of Patients in the ITT Population	N	30	31	30
CNA%	n	25	27	24
	Mean	84.051	58.784	25.676
	STD	7.244	20.569	17.695
	Median	84.050	49.710	29.230
	(Min., Max.)	(61.83, 95.05)	(29.98, 96.14)	(-8.86, 52.27)
Mixed Model Fixed Effect [a]				
Sequence	p-value	0.5287		
Period	p-value	0.2547		
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.				

** Indicates statistical significance at the 0.010 level.

[a] P-values from a semi-parametric mixed model on ranked CNA% values including sequence, period, and treatment group as fixed effects, and patient ID as random effect.

Notes:

1. CNA%= Coefficient of Nitrogen Absorption
2. CNA% has been calculated as follows (in some instances, the CNA% has been calculated over 96 hours instead of 72 hours):

$$\frac{(\text{72-hour protein intake (g)}/6.25) - \text{72-hour nitrogen excretion (g)}}{\text{72-hour protein intake (g)}/6.25} \times 100\%$$

3. The nitrogen excretion value (g/24h) transferred by the Central Lab has been multiplied by 3 before analysis in order to convert it to total nitrogen content.
4. For each patient, Delta is the difference between CNA% Ultrase® MT20 value and CNA% Placebo value.

Source: Table 14.2-3

Although an improvement in the CNA % was observed, the clinical relevance of this is finding unknown. Hence findings regarding the CNA % should not be included in the label to support an indication.

6.1.6 Other Endpoints

The Sponsor also studied 1) the number of bowel movements per day, and 2) proportion of daily stools by characteristic (formed, soft, and watery) between the two treatment groups. The Reviewer did not independently verify these results, which are summarized below based on material taken from the Sponsor's submission. The endpoints have not been validated and their clinical significance is unknown, and the descriptive data are not intended for informing the label. Therefore they are included here only for the sake of completion.

Day 3 of the two Study Drug Treatment Periods is representative of the effects of the treatments on the daily number of stools as reported by patients and includes the largest number of patients reporting this frequency while on both treatments. Treatment with Ultrase® resulted in a mean

of about half as many daily stools as did Placebo Treatment (see Table 18, copied electronically from the Sponsor's submission).

Table 18 Summary of total daily number of bowel movements on Day 3 of treatment (ITT)

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Total Daily Number of Bowel Movements	n	29	30
	Mean	1.5	3.1
	STD	1.0	1.8
	Median	1.0	3.0
	(Min., Max.)	(0, 5)	(0, 7)

Notes:
1. Hypothesis testing of this data was not performed.
Source: Table 14.2-5

Day 4 of the Study Drug Treatment Periods is representative of the effects of treatment on the characteristics of the stools as reported by patients and includes the largest number of patients reporting this frequency while on the Ultrase® MT20 treatment. As shown in Table 19 (copied electronically from the Sponsor's submission), Ultrase® treatment resulted in a preponderance of patients with normal stools (76.19% ± 39.13%) as compared to a much smaller percentage of patients taking placebo (25.71% ± 43.84%). The Placebo resulted in most patients having soft stools (66.73% ± 45.08%).

Table 19 Proportion of total daily stools by characteristic on Day 4 of treatment

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Daily Proportion of Hard Stools (%)	n	28	28
	Mean	11.31	3.57
	STD	27.98	18.90
	Median	0.00	0.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Formed/Normal Stools (%)	n	28	28
	Mean	76.19	25.71
	STD	39.13	43.84
	Median	100.00	0.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Soft Stools (%)	n	28	28
	Mean	12.50	66.73
	STD	29.27	45.08
	Median	0.00	100.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Watery Stools (%)	n	28	28
	Mean	0.00	3.99
	STD	0.00	13.65
	Median	0.00	0.00
	(Min., Max.)	(0.0, 0.0)	(0.0, 66.7)

Notes:
1. For each patient, the daily proportion (%) of Hard stools have been calculated as follows: (Total number of Hard stools on a particular day / Total number of stools on that day) * 100%.
2. For each patient, the daily proportion (%) of Formed/Normal stools have been calculated as follows: (Total number of Formed/Normal stools on a particular day / Total number of stools on that day) * 100%.
3. For each patient, the daily proportion (%) of Soft stools have been calculated as follows: (Total number of Soft stools on a particular day / Total number of stools on that day) * 100%.
4. For each patient, the daily proportion (%) of Watery stools have been calculated as follows: (Total number of Watery stools on a particular day / Total number of stools on that day) * 100%.
5. Hypothesis testing of these data was not performed.

Source: Table 14.2-7

6.1.7 Subpopulations

A significant portion of the target population for PEPs includes pediatric patients with CF, in which there is chronic EPI dating from birth, and treatment can begin as early as one month of age, if not earlier. Current recommendations state that enzyme should be administered to all CF infants who are fed infant formula and solid foods containing macronutrients.[11, 12] As such, data from clinical experience in children are essential to support the appropriate use of these products starting at one month of age (if not earlier). Furthermore, in accordance with the Pediatric Research Equity Act (PREA), applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment--unless the sponsor has obtained a waiver or deferral of pediatric studies (Section 505B of the Federal Food Drug and Cosmetic Act).

The Ultrase® clinical development program has been conducted exclusively in CF patients with EPI. The pivotal study, which provided safety and efficacy information for the TbMP included patients down to eight years of age, though neither one of these youngest patients completed the study (Patient 0102 withdrew consent during Study Drug Treatment Period 2 while he was on Ultrase® treatment; Patient 0103 was a Screening failure, but he was part of the Safety Population). The next older patient in this study was a ten-year-old child. Supportive evidence for safety and efficacy that came from the two studies that used an older formulation not intended for marketing included data from patients as young as seven years of age (Study 96-01), and eight years of age (Study 96-02). As part of this NDA submission the Sponsor provided a pediatric assessment. Data shown in Table 20 (copied electronically from the Sponsor's submission) are for patients for whom complete data were available.

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11 Borowitz D, Grand R, Durie P. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr 1995; 127:681-694.
12 Borowitz D, Baker R, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002; 35: 246-259.

Table 20 Coefficient of fat absorption (CFA %) for patients 10-16 years of age (Studies UMT20CF05-01 and 96-01 and 96-02)

Patient #	Age*	CFA (%) ULTRASE**	CFA (%) Placebo**	Difference % ULTRASE - Placebo
Study UMT20CF05-01				
0104	10	80.87	57.24	23.63
0202	15	90.30	97.12	-6.82
0204	13	92.69	44.07	48.62
0205	15	89.53	78.58	10.95
0207	14	88.51	13.59	74.92
0302	15	92.36	17.14	75.22
0305	16	77.36	63.07	14.29
0901	15	88.86	46.60	42.26
0902	12	83.41	40.47	42.94
1001	16	86.04	93.28	-7.24
1006	16	97.08	84.61	12.47
Mean %CFA	-	87.91%	57.8%	30.1%

*From Study Report Listing 5.1, 5.3.5.1 Study UMT20CF05-01 Appendix 16.2.4, Vol. 14, p. 2
**From Study Report Listing 16.1, 5.3.5.1 Study UMT20CF05-01 Appendix 16.2.6, Vol. 14, p. 175; CFA is defined as: (72-hour fat intake (g) – 72-hour fat excretion (g)) x 100 / 72-hour fat intake (g)

Patient #	Age*	CFA (%) ULTRASE**	CFA (%) Placebo**	Difference % ULTRASE - Placebo
Study 96-01				
A01	9	72.5	51.5	21.0
A02	8	92.2	37.3	54.9
A04	16	88.3	63.9	24.4
A05	14	88.9	69.0	19.9
A06	12	85.5	35.0	50.4
A09	15	99.1	82.8	16.2
A10	15	92.6	51.1	41.4
B02	16	91.9	75.5	16.5
B06	11	83.4	59.9	23.5
F01	12	90.9	59.0	31.9
F04	10	90.8	58.1	32.7
F05	7	89.9	49.9	40.0
F06	13	88.9	55.3	33.5
F09	15	95.0	72.6	22.4
F10	16	90.3	29.9	60.4
Mean %CFA	-	89.3%	56.7%	32.6%
Study 96-02				
C02	11	49.7	-42.5***	92.2
C03	14	64.3	50.7	13.6
C05	16	81.5	63.2	18.3
C06	15	91.9	86.3	5.5
D01	10	78.5	54.5	24.0
D03	13	72.5	66.0	6.6
D08	13	95.9	79.8	16.2
D09	8	91.9	74.5	17.4
E01	13	76.0	55.6	20.4
E02	10	76.0	88.1	-12.1
E04	11	92.4	59.7	32.8
E07	16	93.0	90.5	2.5
E08	11	79.4	38.7	40.7
E09	11	55.9	40.5	15.4
Mean %CFA	-	78.5%	57.5%	21.0%

*From Study Report Listings 16.2.5, 5.3.5.1 Study 96-01, Vol. 4, p. 515; 5.3.5.1 Study 96-02, Vol. 8, p. 471

**Calculated from Study Report Listings 16.2.11A and 16.2.21, 5.3.5.1 Study 96-01, Vol. 4, p. 555, 783; 5.3.5.1 Study 96-02, Vol. 8., p. 504, 681; CFA is defined as: (72-hour fat intake (g) (Days 3-5) – 72-hour fat excretion (g)) x 100 / 72-hour fat intake (g)

***Excretion was greater than the fat intake for this patient

Such is the extent of evidence for efficacy in children studied in the Ultrase® clinical program. Data to date in patients less than twelve years of age are limited, which is not consistent with the use of the product in the post-marketing experience. In a Type C meeting held between the Division and the Sponsor on 16 January 2008, the Division expressed that the two oldest studies conducted by Scandipharm Inc. (Studies 01 and 02) that included younger pediatric patients (≤ seven years of age) could not be used to provide evidence of safety and efficacy because these studies were only available as legacy reports whose data were not available in a reviewable format. Since labeling can only reflect the patient population actually studied (i.e., patients older than eight years), the Division recommended that studies in pediatric patients seven years and younger be initiated as soon as possible so to be able to broaden the treatment population statement in the labeling should Ultrase® be approved. Accordingly, the Sponsor is planning to conduct the following study, which has submitted a draft protocol for Study UMT12CTF0801 titled: "*Efficacy and safety of Ultrase® MT12 in the control of steatorrhea in Cystic Fibrosis (CF) and Pancreatic Insufficient (PI) children Aged 2 to 6 years old.*" Enrollment is expected to begin in the third quarter (Q3) of 2008.

One potential concern about the use of Ultrase® in younger children is the fact that solid oral dosage forms like capsules can be hard for younger patients to swallow. However, Ultrase® MT capsules contain enteric-coated minitablets of pancreatic enzymes, and the delayed-release properties of the product are imparted by the minitablets, not the capsule. In situations where young patients cannot swallow an intact capsule, this formulation allows the capsule to be broken open and the minitablets dispersed in food without impacting the integrity of the enteric coating. The most appropriate dosing for Ultrase® MT Capsules is based on body weight, with a recommended starting dose of 500 lipase unit/kg body weight/meal. Although for younger children who cannot swallow whole capsules, Ultrase® MT Capsules can be broken to release the enteric-coated minitablets, accurate sub-division of the minitablets once the capsule has been opened would be difficult; for this reason, doses of < 1 capsule per meal are not recommended. This limits the use of the lowest strength of Ultrase® (MT12) to a child of 14 kg body weight or higher. To provide for appropriate dosing in infants, the Sponsor is in the process of developing a low dose pediatric formulation of ULTRASE® which would contain (b) (4) lipase units per capsule. This formulation development work is in progress, and the Sponsor has requested a Pediatric Deferral. The purpose of the requested Deferral is to allow for the additional time needed to complete this development, and this request appears reasonable to the Division. As per Section 505B(a)(3)(A)(i) of the Act, the basis for the Deferral is that the product is ready for approval for use in adults and children two years of age and older, and pediatric studies on infants have not yet been completed.

This Reviewer assessed the primary endpoint by gender and by age (<16 and >16), and found no gender or age effect. It was not possible to assess the primary endpoint by ethnicity since there were too few non-Caucasian patients studied. Since CF patients are mostly Caucasian, the homogeneity of race in the clinical development program is not a critical factor. It appears that the only patter that could be seen on subgroup analysis was that the patients who were the most severely affected, gained the most benefit by having an increase in CFA % of at least 30 points, an improvement defined by the medical literature as clinically meaningful.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Due to the time constraint, this Reviewer has not independently verified, but assumes that all patients in the study were treated according to CFF/FDA Guidelines and the patients were titrated on an individual basis within these Guidelines according to symptoms, in which case the dosing regimen would be reflective of the expected clinical use in the post marketing experience. Dosing is to follow the guidelines set by the CFF and FDA due to a safety concern for fibrosing colonopathy (FC). See Section 2.4 Important Safety Issues with Consideration to Related Drugs, and Section 6.1.3.3. Measurement of Treatment Compliance.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In this short-term study, effects of persistence of efficacy and/or tolerance were not studied. However, given the extensive experience of PEP, it has not been reported in the medical literature that persistence of efficacy or tolerance effects have been observed.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Supportive evidence: Studies 96-01 and 96-02

Results of these studies were reviewed in less detail than that for the pivotal trial, as these studies were mainly supportive. The Sponsor's analysis and FDA statistician Dr. Grosser's confirmatory analysis were reviewed. The following is taken from Dr. Grosser's review, paraphrased, with additional clinical comments made by this Reviewer where relevant.

Studies 96-01 and 96-02 were carried out nearly a decade prior to submission of this NDA (last patient completed Study 96-01 on 24 August 1998; and last patient completed Study 96-02 on 29 August in 1999). They were nearly identical in design with the main difference being that Study 96-01 used a higher strength Ultrase® MT20 capsules, and Study 96-02, a lower strength Ultrase MT 12. They were also similar in many ways to study UMT20CF05-010 - except that in these supportive studies, an older formulation of Ultrase® (coated with Eudragit®) - a formulation not intended for marketing - was used. Because the *in vivo* bioactivity/bioavailability testing did not establish comparability linking the two formulations (Ultrase® MT Eudragit® and Ultrase® MT HP-55), the results of these two older studies could not be used to inform labeling for the TbMP. But, they are still relevant being that they could provide supportive evidence for the drug's safety and efficacy, and therefore, are cited and briefly summarized here.

Similar to Study UMT20CF05-01, Studies 96-01 and 96-02 were multi-center, randomized, double-blind, placebo-controlled, crossover-studies designed to evaluate the safety and efficacy of Ultrase® MT in the treatment of steatorrhea in CF patients with a history of EPI. Each study consisted of a diet and enzyme Stabilization Period (7 days) followed by a Treatment Period of approximately six days and then, after a switch of treatments, a second Treatment Period of approximately six days. Patients were randomized to receive the Study Drug Treatment either in the sequence of Ultrase® MT → Placebo, or Placebo → Ultrase® MT. The evaluation of efficacy was based on a within-subject comparison of the CFA % between Ultrase® and Placebo treatment periods; a secondary comparison was the CNA %.

For both Studies 96-01 and 96-02, it was assumed that there would be at least a 30% difference between the Ultrase® MT and Placebo treatment periods with respect to percent fat absorption and percent protein absorption. Further assuming a standard deviation of 30% between Placebo and Ultrase, and a two-sided alpha of 0.05, a sample size of 21 would give a power of 90% to detect a minimum difference of +18 in CFA %.

6.1.10.1.1 Study 96-01

Results for Study 96-01 showed that 31 patients were randomized. Twenty-seven patients (14 on Ultrase MT20 and 13 on Placebo) completed Treatment Period 1, and they constitute what the Sponsor calls the ITT population. Of these, 25 patients completed both treatment periods. Patients ranged from 7 to 36 years of age, with 19 males (70%) and eight females in the ITT population. Twenty-six (96%) were Caucasian. Results for fat and protein percent absorption are shown below in Table 21 (copied electronically from the Sponsor's submission). A difference of +29 in CFA % was seen in improvement with Ultrase® to Placebo, with the results being highly statistically significant.

Table 21 Overall summary results of percent fat and nitrogen absorption in the ITT population of Study 96-01

OVERALL SUMMARY OF PERCENT ABSORPTION – INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=27) [1]**	**Placebo (N=25)**	**Treatment Comparison (p-value)**
Dietary Fat (g)			
Mean ± SD	87.7 ± 10.1	58.7 ± 16.5	0.0001*
Range	46.8 to 99.1	29.9 to 96.2	
N	26	25	
Dietary Protein (g)			
Mean ± SD	88.8 ± 6.1	62.9 ± 18.2	0.0001*
Range	70.3 to 98.7	33.5 to 97.3	
N	26	25	

Source: Table 14.8B
* Significant at .05 significance level
[1] Stool collection for subject F12 was incomplete

6.1.10.1.2 Study 96-02

Twenty-six patients were randomized. Twenty-three patients completed Treatment Period 1 and constitute the (modified) ITT population; twelve patients received Ultrase MT12, and 11 received Placebo during Treatment Period 1. Of these, 22 completed both treatment periods (the evaluable population). Patients ranged from 8 to 36 years of age, with 16 males (70%) and seven females in the ITT population; 20 (87%) were Caucasian. Results for percent absorption are shown below in Table 22 (copied electronically from the Sponsor's submission). The results show that a difference of +33 in CFA % was seen in improvement with Ultrase® to Placebo, with the results being highly statistically significant.

Table 22 Overall summary results of percent fat and nitrogen absorption in the ITT population of Study 96-02

OVERALL SUMMARY OF PERCENT ABSORPTION FOR INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=23)**	**Placebo (N=22)** [1]	**Treatment Comparison (p-value)**
Dietary Fat (g)			
Mean ± SD	79.4 ± 12.5	46.7 ± 35.8	0.0002*
Range	49.7 to 95.9	-51.3 to 90.5	
N	23	22	
Dietary Protein (g)			
Mean ± SD	83.9 ± 11.0	58.4 ±24.8	0.0001*
Range	45.4 to 96.8	-18.1 to 92.7	
N	23	22	

Source: Table 14.8A
* Significant at .05 significance level
[1] Subject C02 protein/fat input was less than protein/fat output

The magnitude of CFA % improvement on Ultrase® MT 20 and 12 using the Eudragit® formulation provides supportive evidence for efficacy, and is within the expected range with that of Ultrase® MT HP-55 and other PEPs in the same drug class.

7 Review of Safety

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

This Reviewer used safety information from the individual double-blind, placebo-controlled clinical studies (Studies 96-01, 96-02, and UMT20CF-05-01) to generate an integrated safety analysis for Ultrase® MT in the treatment of EPI in CF patients seven years and older. Supportive information in the form of spontaneous reporting and publications from the medical literature on PEPs was also reviewed. The Sponsor submitted an original integrated safety summary (ISS) on 31 July 2007, a reorganized version (but containing no new data) on 20 December 2007, and an 120-day Safety Update on 1 February 2008, all of which were reviewed, including the electronic datasets and the Sponsor's interpretation of the safety data.

A brief description of the clinical studies that were used to evaluate safety is as follows.

Studies 96-01 and 96-02
Studies 96-01 and 96-02 assessed Ultrase® MT capsules that contained minitablets coated with Eudragit®; study designs were identical except for the dosage of Ultrase® used as study drug (Ultrase® MT20 and MT12, respectively). These studies were both randomized, double-blind, placebo-controlled, two-week, two-period cross-over studies. Each CF patient was required to

consume a high-fat diet at home, and to be stabilized on an optimized dose of Ultrase® based on clinical observations and symptoms. The high fat diet was to include at least 2 g of fat per kg of body weight daily. During Treatment Period 1, patients were randomized to receive either Ultrase® or Placebo for at least six days; a 72-hour fecal fat test was performed. Patients then entered Treatment Period 2, where they were crossed over to the opposite treatment, i.e., patients who received Placebo were now to receive active study drug and vice versa; a 72-hour fecal fat test was collected during the second six-day treatment period.

Patients were monitored throughout for the occurrence of AEs until the end of the two-week study period. Laboratory studies, physical exams and vital sign measurements were performed on Day 6 of each of the Treatment Periods, and a 24-hour urine collection for creatinine and uric acid was collected on Day 5 of both Treatment Periods. A 24-hour urine uric acid collection was performed because of the concern for hyperuricemia and hyperuricosuria associated with PEP treatment.

Study UMT20CF05-01
The pivotal study, Study UMT20CF05-01 was a randomized, double-blind, placebo-controlled crossover study in CF patients using Ultrase® MT capsules containing minitablets enteric coated with HP55. This was a Phase 3, multi-center trial conducted in two phases: a screening phase and a treatment comparison phase. During the screening phase (up to 11 days) patients were maintained/switched to open-label Ultrase® MT (either Ultrase® MT 18 or 20) to adjust to a stable high-fat diet, defined as 2 g (± 15%) of fat per kg of body weight per day, also taking into account the patient's activity level and appetite. During the Comparison Phase, patients were hospitalized for the two inpatient Study Drug Treatment Periods of six to seven days each. Before each Study Drug Treatment Period there was a Stabilization Period of four days, during which patients consumed the high-fat diet and were treated with a "stabilizing" dose of Ultrase® MT20 titrated to tolerate the high-fat diet. This Stabilized Dose was the dose used for both Stabilizing Periods (Ultrase® MT20) and Treatment Periods of the Study Drug (Ultrase® MT20 or Placebo). Randomization assigned one group of patients to receive Ultrase® MT20 for Treatment Period 1, then Placebo for Treatment Period 2; and, the other group the opposite sequence. A 72-hour fecal fat testing was performed for each of the Treatment Periods. A break of three to six days was taken between the two Study Drug Treatment Periods (i.e., after the end of Treatment Period 1 and before the start of Stabilization Period 2) to provide a break/washout for patients to be liberated from the high-fat diet, during which they could take taking Ultrase® MT 20 at an *ad lib* dose.

Patients were monitored for the occurrence of treatment emergent AEs throughout the study period, including a seven to ten day follow up after discharge of the second Treatment Period. The full reporting study window was from successful screening to ≤ 30 days after the last dose of study medication. During Treatment Periods, laboratory studies, physical exams and vital sign measurements were performed. Unlike for Studies 96-01 and 96-02, a 24-hour urine uric acid collection was not done.

This Reviewer did not review the safety data from the two oldest studies (Study 01 and 02) because only legacy reports were available for them (the data were not in a reviewable format),

and AEs were not collected for Study 02. The Sponsor did not include these two studies in their ISS analysis.

7.1.2 Adequacy of Data

The AE terms in the double-blind, placebo-controlled Studies 96-01 and 96-02 were originally coded in COSTART, but the integrated summary table was recoded using MedDRA v10.0 for the purpose of this submission. The Phase 3 study, UMT20CF05-01 was coded using MedDRA v.9.0. The Sponsor's coding appeared adequate.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

This reviewer pooled data across the three double-blind placebo controlled studies (Studies UMT20CF05-01, and 96-01 and 96-02) to increase the number of patients analyzed for safety. But given that only Study UMT20CF05-01 administered the TbMP product, a separate safety analysis was also performed where possible.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

It appears to this Reviewer that in the randomized, double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01 and 96-02), a total of 94 patients were treated with at least one dose of Ultrase®, which should have constituted the true safety population analysis (Note: The Sponsor submitted the safety analyses on various "modified" safety populations, e.g., patients who completed the study, patients who were randomized, etc. The differences in the numbers of patients between these modified safety populations and the "true" safety population of 94 were small, a handful of patients, which does not change the overall conclusion about the safety profile. Final labeling should reflect the safety experience gathered in studies that were conducted in the TbMP). In these 94 patients, there were 16 patients under the age of 12 (3 patients in Study UMT20CF05-01; 5 patients in Study 96-01; and 8 patients in Study 96-02). The age distribution of the 94 patients in the "true" safety population can be found in Table 23 for Study UMT20CF05-01 and in Figure 2 for Studies 96-01 and 96-02 (Figure 2 was copied electronically from the Sponsor's submission since no electronic datasets for the patient demographics were submitted).

Table 23 Age distribution in Study UMT20CF05-01 (N=36, safety population)

SUBJECT	AGE
0102	8
0103	8
0104	10
0902	12
0204	13
0207	14
0202	15
0205	15
0302	15
0901	15
0301	16
0305	16
1001	16
1006	16
0201	17
0601	18
0304	19
0306	19
1007	19
0502	20
1002	20
0101	21
0503	21
0701	21
0303	23
1003	23
1005	23
0203	24
0501	24
0206	25
0105	27
0505	27
0604	27
0603	34
0602	35
0504	37

Figure 2 Age distribution of the safety population in Studies 96-01 and 96-02

Study 96-01 (N=32, safety population)

SCANDIPHARM, INC. - ULTRASE STUDY, PROTOCOL NO. 96-01

DATA LISTING 16.2.5
DEMOGRAPHICS

SITE	PATIENT NUMBER	TREATMENT SEQUENCE	DATE OF BIRTH	AGE (years)	SEX	RACE
A - DR. STERN	A01	ULTRASE-PLACEBO	(b) (6)	9	MALE	CAUCASIAN
	A02	PLACEBO-ULTRASE		8	FEMALE	CAUCASIAN
	A03	PLACEBO-ULTRASE		19	MALE	CAUCASIAN
	A04	ULTRASE-PLACEBO		16	MALE	CAUCASIAN
	A05	ULTRASE-PLACEBO		14	MALE	CAUCASIAN
	A06	ULTRASE-PLACEBO		12	FEMALE	CAUCASIAN
	A07	PLACEBO-ULTRASE		36	MALE	CAUCASIAN
	A08	PLACEBO-ULTRASE		20	MALE	CAUCASIAN
	A09	PLACEBO-ULTRASE		15	MALE	CAUCASIAN
	A10	PLACEBO-ULTRASE		15	MALE	CAUCASIAN
	A11	ULTRASE-PLACEBO		32	MALE	CAUCASIAN
B - DR. EIGEN	B01	ULTRASE-PLACEBO		19	FEMALE	CAUCASIAN
	B02	PLACEBO-ULTRASE		16	MALE	CAUCASIAN
	B03	ULTRASE-PLACEBO		17	FEMALE	CAUCASIAN
	B04	PLACEBO-ULTRASE		20	MALE	CAUCASIAN
	B05	ULTRASE-PLACEBO		20	FEMALE	CAUCASIAN
	B06	ULTRASE-PLACEBO		11	FEMALE	CAUCASIAN
	B07	PLACEBO-ULTRASE		18	FEMALE	CAUCASIAN
	B08	PLACEBO-ULTRASE		19	MALE	CAUCASIAN
	B09	PLACEBO-ULTRASE		17	MALE	CAUCASIAN
F - DR. DUGGAN	F01	ULTRASE-PLACEBO		12	MALE	CAUCASIAN
	F02	PLACEBO-ULTRASE		15	MALE	CAUCASIAN
	F04	ULTRASE-PLACEBO		10	MALE	HISPANIC
	F05	PLACEBO-ULTRASE		7	MALE	CAUCASIAN
	F06	PLACEBO-ULTRASE		13	MALE	CAUCASIAN
	F07	ULTRASE-PLACEBO		13	MALE	CAUCASIAN
	F08	ULTRASE-PLACEBO		31	MALE	CAUCASIAN
	F09	ULTRASE-PLACEBO		15	FEMALE	CAUCASIAN
	F10	PLACEBO-ULTRASE		16	MALE	CAUCASIAN
	F11	PLACEBO-ULTRASE		16	MALE	CAUCASIAN
	F12	ULTRASE-PLACEBO		22	MALE	CAUCASIAN

Study 96-02 (N= 26, safety population)

SCANDIPHARM, INC. - ULTRASE STUDY, PROTOCOL NO. 96-02

DATA LISTING 16.2.5
DEMOGRAPHICS

SITE	PATIENT NUMBER	TREATMENT SEQUENCE	DATE OF BIRTH	AGE (years)	SEX	RACE
			(b) (6)			
C - DR. STERN	C01	ULTRASE-PLACEBO		17	MALE	HISPANIC
	C02	PLACEBO-ULTRASE		11	MALE	CAUCASIA
	C03	ULTRASE-PLACEBO		14	MALE	CAUCASIA
	C04	PLACEBO-ULTRASE		21	MALE	CAUCASIA
	C05	ULTRASE-PLACEBO		16	MALE	CAUCASIA
	C06	PLACEBO-ULTRASE		15	MALE	BLACK
D - DR. SHERMAN	D01	ULTRASE-PLACEBO		10	MALE	CAUCASIA
	D02	ULTRASE-PLACEBO		17	FEMALE	CAUCASIA
	D03	PLACEBO-ULTRASE		13	MALE	CAUCASIA
	D04	PLACEBO-ULTRASE		22	MALE	BLACK
	D05	PLACEBO-ULTRASE		32	MALE	CAUCASIA
	D06	ULTRASE-PLACEBO		20	MALE	CAUCASIA
	D07	PLACEBO-ULTRASE		36	MALE	CAUCASIA
	D08	ULTRASE-PLACEBO		13	FEMALE	CAUCASIA
	D09	PLACEBO-ULTRASE		8	FEMALE	CAUCASIA
	D10	ULTRASE-PLACEBO		17	FEMALE	CAUCASIA
	D11	PLACEBO-ULTRASE		16	FEMALE	CAUCASIA
E - DR. ACCURSO	E01	PLACEBO-ULTRASE		13	MALE	CAUCASIA
	E02	ULTRASE-PLACEBO		10	FEMALE	CAUCASIA
	E03	PLACEBO-ULTRASE		18	MALE	CAUCASIA
	E04	ULTRASE-PLACEBO		11	FEMALE	CAUCASIA
	E05	ULTRASE-PLACEBO		19	FEMALE	CAUCASIA
	E06	PLACEBO-ULTRASE		22	MALE	CAUCASIA
	E07	PLACEBO-ULTRASE		16	FEMALE	CAUCASIA
	E08	ULTRASE-PLACEBO		11	MALE	CAUCASIA
	E09	ULTRASE-PLACEBO		11	MALE	CAUCASIA

Approximately a third of patients received Ultrase® MT 12 coated with Eudragit®; a third received Ultrase® MT 20 coated with Eudragit®; and a third received Ultrase® MT 20 coated with HP 55 (TbMP). The mean daily Ultrase® dose in the study was approximately 7000-7500 lipase units/kg/day.

Demographic characteristics for the randomized patients (one of the Sponsor's modified safety populations) enrolled in these double-blind, placebo-controlled studies are displayed in Table 24 (copied electronically from the Sponsor's submission). The data illustrate that the majority of randomized patients (n=88) in these studies were Caucasian (81 of 88; 92%) and there was a higher prevalence of male patients (60 patients; 68%) in all three studies. Study patients were generally young (mean ages ranging from 16.5 to 19.6 years of age) with a mean history since diagnosis of CF from 15.9 to 19.2 years.

Table 24 Demographic of safety populations in the placebo controlled studies

Variable	Study	96-01 n=31*	96-02 n=26*	UMT20CF05-01 n=31*
Age (years)	mean (SD)	16.9 (6.6)	16.5 (6.5)	19.6 (6.6)
	range	7.0 - 36.0	8.0 – 36.0	8 - 37
Weight (kg)	mean (SD)	50.9 (17.5)	49.8 (14.7)	55.56 (11.61)
	range	19.0 - 91.0	26.8 – 80.0	31.1 - 88.0
Height (cm)	mean (SD)	158.6 (18.1)	157.8 (16.1)	164.3 (13.2)
	range	113.0 – 183.0	127.0 – 185.4	1.22 - 1.89
Years since CF diagnosis	mean (SD)	16.2 (6.8)	15.9 (6.4)	19.2 (7.4)
	range	4.0 – 35.0	6.0 – 33.0	3 - 37
Gender, n (%)	male	23 [74]	17 [65]	20 (64.5)
	female	8 [26]	9 [35]	11 (35.5)
Race, n (%)	Caucasian	30 [97]	22 [85]	29 (93.5)
	Black	0	2 [8]	2 (6.5)
	Hispanic	1 [3]	1 [4]	0
	Caucasian/Black	0	1 [4]	0

*All randomized patients
Source: 5.3.5.1 Study 96-01, Vol. 3, p. 77; Study 96-02, Vol. 7, p. 77; Study UMTCF05-01 14.0 Tables, Vol. 11, p. 2

A major limitation of the safety data is that patients younger than seven years were not studied. The data in the Ultrase® MT clinical program were also limited by other factors, including small study size, use of only one study in the TbMP, homogeneous population, and short study duration. However, for the purpose of this NDA safety review since this application is a 505(b)(2), it is acceptable that the Ultrase® MT clinical program is limited to short-term efficacy and safety studies. The long-term safety of PEPs has been established over the many years of their use and this application relied on the published medical literature for full descriptions of AE profiles.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients were titrated to relief of symptoms, and this Reviewer presumes that patients' dosing during the studies remained within the CFF/FDA guidelines, and if that was true, this Reviewer is in the opinion that the Sponsor

has adequately addressed the issue of dose response. Of note, the Sponsor proposed to market three strengths of Ultrase® MT (MT12, 18, and 20). In the TbMP, only Ultrase® MT 18 or 20 was used in the Screening Period, and only Ultrase® 20 was used in the Ultrase® MT Study Drug Treatment Period.

A Pediatric Deferral to allow the Sponsor to develop an infant-appropriate formulation to be administered to children less than two years of age is a reasonable approach and should be granted.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not required to support the EUR-1008 clinical development program. In addition, this was a 505(b)(2) application thus no special animal or in vitro testing was required.

This Reviewer will not attempt a general assessment of the preclinical program, only to comment that preclinical testing appeared adequate to explore certain potential adverse reactions (i.e., fibrosing colonopathy and the high dosing of excipients and impurities). Please see Section 4.3 Preclinical Pharmacology/Toxicology, and FDA pharmacology-toxicologist Dr. Joseph's review for details.

7.2.4 Routine Clinical Testing

Routine clinical testing of study patients, including efforts to elicit adverse event data and monitor laboratory parameters, vital signs, and physical exams appeared adequate both in terms of the methods and the frequency of testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Knowledge of how a drug is metabolized and excreted is critical to anticipating safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions. PEPs are locally acting agent in the gastrointestinal tract, and therefore are not systemically absorbed. The Sponsor conducted a dog study, using radio-label amylase, to allow for increased sensitivity in the detection of intestinal absorption. The results indicated the absorption of amylase was either "negligible or completely absent." Since PEPs act locally in GI tract and are not systemically absorbed, so absorption, distribution, metabolism and elimination (ADME) assessments were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following statements apply to Ultrase® as well and are taken directly from the Clinical Review by FDA clinical reviewer Ethan Hausman, M.D. for Creon®, however the statements have been paraphrased to suit Ultrase® by this Reviewer.

Rare cases of fibrosing colonopathy (FC) have been reported with PEP use, and are thought to be associated with high-dose PEP administration in younger patients. Given the severity of this

diagnosis, surveillance for FC in PEP clinical development program is relevant to the assessment of safety in this class of medications. No instances of FC were reported in the Ultrase® ISS, but there are limitations in the safety surveillance program; and, conclusions regarding the adequacy of FC case detection are not possible for several reasons. First FC is a histopathologic diagnosis and routine surveillance with colonoscopy and biopsy was not performed in any study. Second, while FC is commonly described as a symptomatically severe and acute process, literature suggests it may actually have a chronic, indolent course; therefore, though severely symptomatic cases might have come to clinical attention during safety assessments, incipient cases might not have been recognized. Third, though fibrosing colonopathy is classically described following high-dose lipase treatment, the doses of Ultrase® administered were within current guidelines promulgated to decrease the risk of FC. Fourth, though the time of exposure required developing FC is undetermined, the short duration of the studies (two weeks) may not have provided a long enough exposure to precipitate FC. Finally, cases of FC in the medical literature appear to have been reported only sporadically. The population studied was relatively small and given the rarity of FC may not have been large enough to detect an FC safety signal. Therefore, this Reviewer believes that although there were no obvious cases of FC reported in this NDA, no conclusions can be drawn regarding the adequacy of FC case detection for the overall ISS population, and monitoring for FC is likely best performed in the post-marketing setting. The issue regarding FC should be included in the label.

It has also been reported that hyperuricemia/hyperuricosuria may be associated with PEP use, which is thought to be related to the purine content of pancreatic extracts from which the PEPs are produced. As more evidence becomes available, it may be relevant to follow this trend in patients with impaired liver function commonly seen in older patients with CF and in patients with CP. The finding might also be relevant in patients with impaired renal function and/or impaired uric acid metabolism (e.g., gout). Given the small study population and short duration of studies, it is unlikely that a single case of clinically significant hyperuricemia or hyperuricosuria would have been seen. The issue regarding hyperuricemia/hyperuricosuria, like FC, should be included in the label and be followed with special attention as part of worldwide Pharmacovigilance in the post-marketing setting.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during any of the short-term studies supporting this submission.

7.3.2 Nonfatal Serious Adverse Events

There were eight SAEs—and except for one case of newly diagnosed diabetes, all were either GI or respiratory related. All were likely CF related.

Study 96-01
One patient experienced abdominal cramping due to obstruction during Placebo treatment. Another patient was diagnosed with pulmonary exacerbation of CF during Placebo treatment.

One patient was diagnosed with diabetes mellitus during the screening period while on Ultrase® MT20. None of these events appeared to be related to Ultrase® treatment.

Study 96-02
No SAEs were reported.

Study UMT20CF05-01
There were two patients (Patient 0103 and 0603) who experienced SAEs during Screening, at which time they were on open-label Ultrase® MT18 or MT20. One patient experienced worsening chest x-ray attributed to pulmonary exacerbation of CF, which was successfully treated with antibiotics. The other patient experienced hemoptysis, also diagnosed as CF-related pulmonary exacerbation, which also resolved with standard medical treatment.

Three patients experienced SAEs within the reporting study window (from successful Screening to ≤ 30 days after the last dose of study medication). One patient (Patient 0505) experienced a CF-related pulmonary exacerbation, an acute bronchiectasis caused by methicillin-resistant *Staphylococcus aureus (MRSA)* and *Pseudomonas aeruginosa* during the Placebo treatment. The two other patients experienced SAEs after returning to using their usual pancrelipase product following study discharge. Patient 0602 experienced dyspnea, productive cough, chills, nausea, vomiting, and abdominal pain, as well as non-serious hemoptysis; Patient 1005 experienced cystic fibrosis lung, hypokalemia, and lymphadenopathy.

7.3.3 Dropouts and/or Discontinuations

Ten patients dropped out due to an AE/SAE, all related to either GI or respiratory symptoms. All appeared to be related to the underlying disease.

Study 96-01
In Study 96-01, SAEs caused three patients to withdraw from the study. While taking Placebo, one patient experienced intestinal obstruction and another reported increased cough; while on Ultrase® therapy during Screening, one patient was diagnosed with diabetes mellitus, identified during the Screening blood work as a concurrent medical condition.

Study 96-02
In Study 96-02 three patients were withdrawn due to non-serious AEs while on Placebo: one due to intestinal obstruction, another due to an intestinal disorder, and a third due to a rectal disorder.

Study UMT20CF05-01
In Study UMT20CF05-01, two patients on open-label Ultrase® failed Screening due to an SAE (one patient experienced worsening chest x-ray abnormality due to CF pulmonary exacerbation, and the other person experienced hemoptysis diagnosed as a CF-related pulmonary exacerbation). One patient experienced SAEs resulting in discontinuation during the study while on the Break Periods between treatment periods (CF lung, bronchiectasis, upper respiratory tract infection, gastrointestinal infection, non-serious vaginal infection, non-serious malnutrition); this patient having received Placebo during Treatment Period 1, which preceded immediately the Break Period. Two other patients experienced non-serious AEs while on Placebo that also

resulted in study discontinuation (abdominal pain in one, and abdominal pain, flatulence, and steatorrhea in the other).

7.3.4 Significant Adverse Events

There were no other significant Adverse Events reported.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns. The issues that have already been discussed elsewhere in this Review regarding fibrosing colonopathy, hyperuricemia or hyperuricosuria, and the safety of Eudragit® coating are of concern to all PEPs, and are not specific to this PEP or submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the pooled safety analysis of the three randomized, double-blind, placebo-controlled studies (UMT20CF05-01, 96-01 and 96-02), the most frequently observed AEs were predominantly gastrointestinal (GI) related, as would be expected in a CF patient population. The most common AEs experienced by patients in during the Ultrase® Study Drug Treatment Period were flatulence (experienced by 26% of patients), abdominal pain (17%), headache (11%), and diarrhea (10%). Of note, these gastrointestinal AEs occurred at a greater incidence in patients during the Placebo Study Drug Treatment Period: flatulence (44%), abdominal pain (50%), and diarrhea (15%), giving support to the hypothesis that these GI AEs were related to the underlying disease, and that without treatment (during Placebo administration), these events reflect a lack of treatment efficacy rather than an AE profile that might have been related to Ultrase® treatment.

Table 25 (copied electronically from the Sponsor's submission) lists the most common AEs affecting ≥ 2% of patients on Ultrase® and occurring in more patients on Ultrase® than placebo in combined data from the double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01, and 96-02). This Reviewer notes that headache occurred in almost twice as many patients (11%) during the Ultrase® Study Drug Treatment Period than during the Placebo (6%).

Table 25 Most common adverse events affecting ≥ 2% of patients on Ultrase® and occurring in more patients on Ultrase® than Placebo: combined data from the double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01 and 96-02)

Treatment	Combined ULTRASE® Number of patients (%) n=82	Combined Placebo Number of patients (%) n=84
MedDRA SOC		
Preferred Term		
Nervous System Disorders		
Headache	9 (11)	5 (6)
Dizziness	2 (2)	1 (1)
Respiratory, Thoracic, And Mediastinal Disorders		
Cough	4 (5)	3 (4)
Epistaxis	2 (2)	1 (1)
Pharyngolaryngeal pain	2 (2)	1 (1)
Gastrointestinal Disorders		
Constipation	4 (5)	3 (4)
Infections And Infestations		
Pharyngitis	2 (2)	0 (0)
Source: Appendix 2.7.4.7 Table 2.7.4.7-4		

This Reviewer noted that the AEs profiles for the pivotal study and the bioactivity/bioequivalence study were similar to that of the pool analysis of the three double-blind, placebo-controlled studies[13]. Safety information (predominantly AE collection) obtained in the BA study that was of limited utility given the design of the study and the small numbers of patients exposed to two, single-doses of Ultrase®.

In summary, the overall AE profile assessment is that no new safety signal attributable to Ultrase® has been identified in the clinical review (with the possible exception that headache occurred in more patients during the Ultrase® treatment period than in Placebo). Most AEs were likely related to the underlying disease, and were either GI or respiratory related. It should be kept in mind that these short-term safety studies could only give limited data on the safety profile of the product, and they are to be supplemented with information from the post-marketing Pharmacovigilance experience, should the product be approved and marketed.

13 A summary of AE by system organ class and preferred terms of the pivotal study (UMT20CF-05-01) can be found in Section 9.6 Appendix 3.

7.4.2 Laboratory Findings

This Reviewer found that there were no clinically significant mean changes for any hematology, chemistry, or urinary parameters that could be attributed to Ultrase® treatment in the three placebo-controlled studies.

The Sponsor notes the following observations:

- In Study 96-01, it was noted that patients receiving Ultrase® MT20 experienced a +28.83 mg mean change (28.83 ± SD 267.48) in urine uric acid within a 24-hour collection period, compared with a mean change of -23.17 mg (-23.17 ± SD 316.16) for patients receiving Placebo although it was also observed that the standard deviations of these values were more than ten times greater than their means, indicating a likely contribution of outliers. Moreover, in the opinion of this Reviewer, this magnitude of increase is unlikely clinically significant given the wide range of the normal value. (NIH normal values range from 250 to 750 mg/24 hours).
- Similarly in Study 96-02, patients while receiving MT12 had a statistically significant mean increase from Screening in uric acid (112.87 ± SD 200.64 mg/24hr; p=0.018) while the Placebo treatment results in a significant mean decrease (-93.70 ± SD 200.64 mg/24 hrs; p=0.036), a differential effect that was statistically significant for the treatment comparison (p=0.001).
- However, in Study UMT20CF05-01, there were no clinically meaningful effects of either Ultrase® or Placebo treatment on mean spot urine uric acid concentration (a 24-hour urine collection for uric acid was not performed for this study). The significance of the differences seen in Studies 96-01 and 96-01 using the Ultrase® MT Eudragit® formulation in evaluating what may be the potential implication of this in the Ultrase® HP55 formulation is unknown.
- In Study UMT20CF05-01 a few patients while on Ultrase® (2; 6.9%) and more patients while on Placebo treatment (9; 30%) developed green urine likely due to the FD&C blue #2 dye stool marker ingested as part of the 72-hour stool sampling process. It is unknown why more patients while on Ultrase® would experience this affect, which is likely an artifact.

7.4.3 Vital Signs

In Studies 96-01 and 96-02, post-treatment vital signs were not recorded. A summary of the Treatment Period physical examinations demonstrated no clinically significant changes between the Screening and the Treatment Periods. In Study UMT20CF05-01, there were no effects of Ultrase® treatment on mean vital signs.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected or examined because PEPs are products that act locally in the GI tract, and are not expected to have systemic effect, or to affect cardiac function.

7.4.5 Special Safety Studies

There were no special safety studies performed during the Ultrase clinical development program.

7.4.6 Immunogenicity

Ultrase® is not systemically absorbed, and there were no assessments performed specifically related to immunogenicity (i.e., antibody testing).

7.5 Other Safety Explorations

No other safety explorations were performed.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Ultrase® is not systemically absorbed and human carcinogenicity studies were not part of the clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

FDA Pharmacology Toxicology Reviewer (Dr. Joseph) recommends that the following statement be included in the label:

"Animal reproduction studies have not been conducted with Ultrase®. It is also not known whether Ultrase® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ultrase® should be given to a pregnant woman only if clearly needed. It is not known whether this drug is excreted in human milk. Caution should be exercised when Ultrase® is administered to a nursing mother."

Ultrase® is almost certainly going to be used by women of reproductive potential and may be used by pregnant and lactating women. The effect of Ultrase® and the excipients on the fetus is unknown, therefore a request for a pregnancy and lactation registry should be considered at the time of approval.

7.6.3 Pediatrics and Effect on Growth

These short-term studies are not capable of elucidating whether Ultrase® MT might pose a safety issue in the growth and development in pediatric patients. But, based on long-term information from public literature, pediatric patients with CF derive benefits from PEP treatment in terms of growth, development, functional status, and survival: the standard of care is that PEP treatment should be started as soon as CF is diagnosed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The following is taken from the Sponsor's clinical safety summary:

Acute toxicity determination in animals has not been possible since the maximum dose that could be given orally produced no toxic reaction. In chronic feeding tests with a related product, rats developed swollen salivary glands. This is believed to be due to a proteolytic activity of the pancreatic enzyme resulting in mucosal irritation caused by tissue digestion. No acute toxic reactions have been reported. Extremely high doses of PEPs have been associated with hyperuricemia and hyperuricosuria. Over dosage of pancreatic enzyme concentrate may cause diarrhea or transient intestinal upset.

Ultrase® is not known to be subject to drug abuse.

Ultrase® is not known to cause withdrawal or rebound signs or symptoms.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarketing Experience

Ultrase® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been commercially available on the U.S. market since November 1991, first by Scandipharm Inc., then by Axcan Inc.

The Sponsor of this NDA, Axcan Pharma Inc., has been marketing Ultrase® MT Capsules since August 1999 in the U.S. Ultrase® is currently marketed by the Sponsor in Canada and by distributors in Argentina, Brazil, Chile, and Costa Rica. Few adverse events have been reported during this time, either in the literature or directly to the Manufacturer or Sponsor. Nevertheless it should be mentioned that since the product has not been under an NDA in the US, and therefore has been essentially unregulated, no Pharmacovigilance requirements have been set forth, making it likely that AEs are grossly underreported.

Ultrase® is not absorbed into tissues or the general circulatory system, and therefore, systemic reactions to pancrelipase are unlikely to occur. The enzymes in Ultrase® are digested within the stomach and intestinal lumen and are metabolized as dietary protein. For these reasons, Ultrase® is not likely to have effects such as carcinogenesis or effects on fertility or reproduction. The effects of the excipients on these functions are unknown.

In the 16 years that Ultrase® has been marketed, there have been no marketing suspensions or restrictions on the distribution of pancrelipase or changes in target population or indications due to safety reasons. In a January 1994 publication, Smyth et al, described five children with cystic fibrosis in the United Kingdom who had switched from standard strength enteric-coated

formulation to high-strength products, 12 to 15 months before presentation with meconium ileus equivalent that failed to respond to medical management.[14] In response to this study, many high strength enzyme preparations (i.e., those containing >20,000 IU lipase/capsule) were withdrawn from the market by pharmaceutical companies in the U.S.[15] The higher strengths Ultrase® MT Capsules (MT24 and MT30) were voluntarily discontinued by Scandipharm Inc. in 1994.
The safety of Ultrase® from post-marketing reports and literature has been discussed extensively by the Sponsor in the NDA submission with regards to the following:

1. Postmarketing reports for Ultrase® from Axcan's Drug Safety Database.

2. Literature review of experimental and controlled studies and case reports. The studies/reports were sorted according to the associated adverse event:

- Hypersensitivity
- Hyperuricosuria and hyperuricemia
- Intestinal obstruction and stricture (fibrosing colonopathy)
- Esophageal injury
- Other gastrointestinal related adverse effects
- Treatment failure or nutrient interactions

Axcan Pharma Inc. markets Ultrase® as well as Viokase® and Panzytrat®, two other formulations of pancreatic enzymes. The Sponsor submitted a discussion on the post-marketing experience of Ultrase® and other formulations of pancreatic enzymes from the drug safety database maintained by Axcan Pharma Inc. and its subsidiaries. The drug safety database includes spontaneous cases from health care professional and non-health-care professional as well as cases from scientific literature and regulatory authorities. Axcan Pharma Inc. performed a reconciliation process with the World Health Organization's (WHO's) Vigibase in February 2007. During this process, the Vigibase adverse event cases involving Ultrase®, Viokase® and unspecified formulation of pancrelipase were included in the Axcan Pharma Inc. safety database.

An estimate of the patient exposure to Ultrase® MT Capsules was calculated by the Sponsor for October 1999 to January 2007 from the number of product units distributed in the US. While Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile, Costa Rica and Canada), US sales overwhelmingly constitute the greatest percentage globally ([redacted] (b) (4) %). Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1) The majority of patients taking Ultrase® ® MT Capsules for the treatment of steatorrhea are CF patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years; and, 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis

14 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86
15 FitzSimmons, SC., Burkhard, GA, Borowitz, D, et al. High-dose pancreatic-enzyme supplement and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997; 336: 1283-1289.

Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally sit between the 20th and 40th percentile for weight.[16] Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts for males and females between the ages of 2 to 20 years.

2) A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzyme supplementation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from Ultrase® MT capsule supplementation was assumed for calculation purposes.

3) It was assumed that patients would be consuming a total of four meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for Ultrase® MT12, Ultrase® MT18 and Ultrase® MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. Table 26 (copied electronically from the Sponsor's submission) lists U.S. unit sales information for Ultrase® MT Capsules as well as the calculation of patient-exposure-years.

16 Cystic Fibrosis Foundation Patient Registry: Annual Data Report 2004, Vol. 17

Table 26 US unit sales of Ultrase® MT capsules in the period 2000-January 2007* and patient exposure

	MT12 100 ct	MT18 100 ct	MT20 100 ct	MT20 500 ct
	Units	Units	Units	Units
October 1999 – September 2000	(b) (4)			
October 2000 – September 2001				
October 2001 – September 2002				
October 2002 – September 2003				
October 2003 – September 2004				
October 2004 – September 2005				
October 2005 – September 2006				
October 2006 – January 2007				
Total				
Total number of capsules				
Number of days of treatment	3,052,992	2,686,357	6,534,824	6,291,232
Number of years of treatment	8,364	7,360	17,904	17,236
Total number of patient treatment years	50,864			

*Unit sales for ULTRASE® MT capsules are presented for the time period 2000 – January 2007. ULTRASE® MT capsules have been marketed by Axcan Scandipharm Inc. from August 1999.

In the seven-year period (October 2999 to January 2007), US sales figures totaled (b) (4) units of Ultrase® MT12 in 100 ct bottles, (b) (4) units of Ultrase® MT18 in 100 ct bottles, (b) (4) units of Ultrase® MT20 in 100 ct bottles and (b) (4) units of Ultrase® MT20 in 500 ct bottles. The estimate of the patient exposure between October 1999 and January 2007 is therefore approximately 50,864 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of three meals and two snacks per day

Reviewer's comment:
The exposure has been significant, but only relatively few AEs have been reported in the Pharmacovigilance database, as shown in Table 27 (copied electronically from the Sponsor's submission). The most commonly reported AEs were GI system related. Most of the events reported during post-marketing experience were assessed as non-serious. The types of AEs were similar to what has been reported with PEPs in general.

As mentioned above, it is likely that AEs have been grossly under reported because the product has not been approved under an NDA so the reporting requirement has been nil. The data accompanying spontaneous reports are often incomplete and the total number of reactions occurring during post-marketing experience is unknown. In other words, considering that post-marketing surveillance is essentially based on voluntary reporting from health professional and

customers, the frequency provided in the Table 27 should not be used to estimate the incidence of an event in the overall population treated with pancrelipase.

Table 27 Adverse events (preferred term) recorded for pancreatic enzymes in the Axcan Pharma Safety Database classified by system organ class

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Lymphadenopathy	2
GASTROINTESTINAL DISORDERS	
Abdominal discomfort	10
Abdominal pain	13
Abdominal pain upper	3
Abnormal faeces	6
Anorectal disorder	2
Ascites	1
Colitis	4
Constipation	6
Diaorrhea	23
Diarrhoea haemorrhagic	1
Dyspepsia	3
Faeces discoloured	1
Fibrosing colonopathy	11
Flatulence	9
Frequent bowel movements	7
Gastric disorder	1
Gastrointestinal disorder	1
Gastrointestinal haemorrhage	3
Gastrointestinal inflammation	1
Gastrointestinal necrosis	1
Ileitis	1
Ileus	1
Intestinal functional disorder	1
Intestinal obstruction	12
Intestinal perforation	1
Intestinal stenosis	7
Intussusception	1
Lip blister	1
Malabsorption	4

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
GASTROINTESTINAL DISORDERS (CONT'D)	
Melaena	3
Mouth ulceration	1
Nausea	4
Oesophageal stenosis	1
Oesophagitis	1
Oral pain	3
Rectal haemorrhage	1
Steatorrhoea	8
Stomach discomfort	2
Stomatitis	2
Tongue ulceration	1
Vomiting	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Drug ineffective	15
Drug ineffective for unapproved indication	1
Drug interaction	1
Drug intolerance	1
Fatigue	1
Feeling abnormal	1
Granuloma	1
Hunger	1
Malaise	1
Non-cardiac chest pain	1
Pain	3
IMMUNE SYSTEM DISORDERS	
Hypersensitivity	1
INFECTIONS AND INFESTATIONS	
Rash pustular	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Oral administration complication	1

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
INVESTIGATIONS	
Blood glucose increased	2
Liver function test abnormal	1
Medication residue	1
Pancreatic enzymes increased	1
Prothrombin level decreased	1
Weight decreased	2
Weight increased	1
METABOLISM AND NUTRITION DISORDERS	
Dehydration	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Growth retardation	1
Muscle spasms	1
Musculoskeletal chest pain	1
NERVOUS SYSTEM DISORDERS	
Dizziness	2
Hyperaesthesia	1
Paraesthesia	1
Syncope	1
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	
Abortion	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Throat irritation	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Blister	1
Dermatitis diaper	1
Erythema	2
Pruritus	3
Pruritus generalised	1
Rash	6
Skin exfoliation	1
Urticaria	1

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

The Sponsor received 17 individual reports assessed as serious. The SAE case reports are listed below.

Eleven cases of fibrosing colonopathy (FC) were reported from spontaneous notification (10 cases) and literature (1 case). These cases were reported in CF patients who were taking multiple PEPs including Ultrase®. FC has been reported in CF patients treated with both high and lower-strength enzyme supplements.[17]

Reviewer's comment:
The Sponsor has not specified whether there were cases of FC reported since the release of the CFF/FDA Guidelines. It is not also not known whether there are other risk factors for FC, such as whether patients who are younger (i.e., with lower body weight) might be at greater risk.

Three reports involving an unspecified formulation of PEPs were received from the WHO Vigibase database and were assessed as serious by the initial reporter. These cases include: diarrhea, abdominal distension and weight increase in one patient, weight decreased, pain and malabsorption in another patient, as well as stomach discomfort, diarrhea, abdominal pain, pain, nausea, malaise, frequent bowel movements, dizziness and dehydration in the third patient.

One case of three episodes of intestinal obstruction requiring hospitalization was reported in a pediatric patient who was treated with Ultrase®. The patient was dispensed a three-month supply of the drug that was not stored in the original container. As per the reporter's narrative, the treating health professional stated that the obstruction episodes were related to degraded enzyme ingestion.

One case of intussusception was reported in a 15-year-old patient treated with Ultrase® as well as Pancrease®. The patient was switched to Ultrase®, used it for nine days and was switched back to his previous PEP formulation (Pancrease®). One week later, the patient was diagnosed with intussusception. The patient was treated with ileostomy, received total parenteral nutrition (TPN) and was recovering from the event at the time of the report.

One case of fatal intestinal perforation was reported in a 4-year-old patient who was treated with generic formulation of pancrelipase as well as Ultrase®. This report was received from the father of the patient and was not "medically confirmed."

17 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86

9 Appendices

9.1 Literature Review

The Sponsor conducted a literature review on safety related to Ultrase® pertaining to the issues of hypersensitivity, hyperuricosuria and hyperuricemia, intestinal obstruction and stricture, esophageal injury, other gastrointestinal-related adverse effects, treatment failure, and nutrient interactions. Extensive citation of literature has been provided, which is beyond the scope of this review to copy or describe in depth; therefore, the reader is referred to the NDA, under section 2.7.4 Summary of Clinical Safety for details and for specific references. However, the Reviewer highlights the following points to be considered and negotiated with the Sponsor at the time of labeling negotiation, should this NDA be approved in a future review cycle.

1. Hypersensitivity: Although case reports or experimental/controlled studies demonstrating hypersensitivity associated specifically with Ultrase® have not been published, the literature contains many reports of hypersensitivity associated with various other PEPs. The reaction is thought to be IgE-mediated because specific IgE antibodies against the extracts have been identified. All reported hypersensitivity type reactions have been due to inhalation of pancreatic enzyme powder. Symptoms included skin reactions such as urticaria and pruritus, and respiratory reactions such as wheezing and dyspnea. The potential for hypersensitivity reactions has led to the recommendation in the prescribing information for Ultrase® that it not be crushed or chewed prior to ingestion. There is also a specific warning for individuals who may be allergic to pork proteins. For younger pediatric patients who will be dispensed the content of the capsules as powder form to be sprinkled on and dispersed in food (because they cannot swallow capsules), a warning statement about hypersensitivity reactions might be included in the labeling.

2. Hyperuricemia and hyperuricosuria: Uric acid is the metabolic product of nucleic acids, a contaminant found in a variety of pancreatic enzyme formulation, which is ultimately excreted by the kidneys. Because of the low solubility of uric acid, it will precipitate in acidic urine (pH 4.5-6). Therefore, a patient with hyperuricosuria (urinary excretion of uric acid >800 mg/1.73 m^2/24 h) is at risk of uric acid crystallization and damage to the renal tubules. Hyperuricemia is the term applied to settings in which the serum urate concentration is elevated, but neither symptoms nor signs of urate deposition have occurred. Although no studies specific to Ultrase® have been reported, hyperuricosuria and hyperuricemia have been described in patients receiving large doses of pancreatic supplements. Currently marketed enteric-coated PEPs are not expected to cause hyperuricosuria or hyperuricemia, however, because these formulations are more pure and the urate load from enteric coated enzymes is substantially less compared to non-enteric coated preparations, since fewer capsules are used. Furthermore, it is unclear whether the nucleic acid contaminants of the products or an unrecognized manifestation of CF causes the hyperuricosuria. It appears that, in some CF patients, hyperuricemia and/or hyperuricosuria may actually be part of the disease complex. However, in other patients, it appears that PEPs caused these side effects. Therefore, it may be prudent to

evaluate uric acid metabolism in CF patients, who consume large amounts of lipase units per meal on a daily basis. Unfortunately the medical literature does not provide a specific threshold for lipase units beyond which more intensive evaluation of uric acid is warranted.

3. Intestinal Obstruction and Stricture: There have been reports of fibrosing colonopathy in patients receiving high doses of PEPs. Fibrosing colonopathy is characterized pathologically by dense submucosal fibrosis which leads to narrowing and shortening of the colon. The disease begins in the cecum and ascending colon, and extends distally, and can eventually progress to involve the entire colon. Damage to the colon appears to be irreversible. Clinically, the presenting symptoms of fibrosing colonopathy include chronic abdominal pain particularly after meals, abdominal distension, a change in bowel habits, bloody stools and failure to thrive. In the later stages of the disease, patients develop vomiting and signs of subacute or acute intestinal obstruction. Symptoms of fibrosing colonopathy usually present within 12 months of starting high-dose pancreatic enzyme therapy but the pathogenesis of fibrosing colonopathy is still unclear. Risk factors noted in case-control studies include high-dose PEP, younger age (2-13 years), a history of gastrointestinal symptoms, prior gastrointestinal surgery, use of histamine H_2 receptor blockers, corticosteroids and recombinant human deoxyribonuclease. Other studies have suggested a role for the enteric coating of the microspheres in some preparations, in particular, the methacrylic acid and ethylacrylate copolymer Eudragit® L30 D-55, but this role remains controversial.[18] Potential etiological factors for fibrosing colonopathy may, therefore, include toxic damage by either the high-dose enzymes themselves, impurities or the coatings. In addition, an immune-mediated mechanism of tissue damage through an antigenic response to the porcine enzymes has been suggested.[19] Increased intestinal permeability, as is observed in CF, may also contribute to the development of fibrosing colonopathy. Epidemiological case-control studies have supported an association between higher doses of PEPs and increased risk. High-strength formulations, which contained 20,000 U or more of lipase per capsules, first became available in 1991, and were intended to improve patient compliance by decreasing the number of capsules needed each day. In 1994, there were three separate reports of CF patients with symptomatic colonic submucosal fibrosis, all of whom had been started on high strength enzymes in the 12 to 20 months prior to diagnosis. Intake of >6,000 lipase units/kg/meal or >10,000 lipase units/kg per day are most often associated with this development. The Cystic Fibrosis Foundation and the FDA surveyed CF centers to determine their experience with fibrosing colonopathy from 1991 through 1993; 45 cases were reported, 15 of which met a formal case definition. Since then, additional case reports have appeared occasionally in the literature. Several workshops have been organized to decide how to use pancreatic enzyme supplements in light of the reports of fibrosing colonopathy. It was agreed that these products are highly valuable for the management of nutrition in CF children, and their use should continue. Recommendations by the Cystic Fibrosis Foundation in conjunction with the FDA

18 FitzsSimmons SC, Burkhard, GA, Borowitz, D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997; 336: 1283-9.
19 Lee, J, Wan, I, and Durie, P Is fibrosing colonopathy an immune mediated disease? Arch Dis Child 1997; 77:66-70

included keeping doses to a range of 500 to 2,500 lipase units/kg per meal, and to keep doses below a maximum of 10,000 lipase units/kg/day. The enteric-coated pancrelipase has been recommended due to the achievement of the desired pharmacological activity at the relative lower dosage. Ultrase® MT capsules are currently manufacture with HP55 and are not methacrylic acid as the enteric-coating, (b) (4)

4. Esophageal Injury: A single case report of odynophagia and endoscopic documentation of an esophageal ulcer appears in the literature. In this patient, part of a series of 17, with the other 16 having different types of medication involved, odynophagia prompted endoscopic evaluation. An esophageal ulcer was documented with particles of the PEP (Pantozyme®) discovered in the ulcer base. Other causes of esophageal ulcer (e.g., carcinoma, herpes simplex, cytomegalovirus and moniliasis were excluded by appropriate testing.

5. Other Gastrointestinal Related Adverse Effects: The Sponsor submitted various sporadic case reports in the literature of other gastrointestinal related adverse effects, including the following: three cases in which prolonged retention of PEP powder in the mouth or chewing of enteric-coated tablets by children caused mouth ulceration and stomatitis; four cases of dryness of the mouth; one case of intolerance to PEP (the child vomited the drug while ingesting); unspecified number of cases of nausea, cramping and/or diarrhea; unspecified number of cases of severe constipation from too rapid increase in enzyme dosage; unspecified number of cases of peri-anal irritation from too rapid passing of significant enzyme activity in the stools due to excessive dosing or too rapid intestinal transit time.

6. Treatment failure: Although not specific to Ultrase®, treatment failure with the use of enteric-coated pancrelipase products has been reported. Three patient cases reported treatment failure after using generic pancrelipase capsules. The patients were diagnosed with CF and the pharmacists had substituted generic pancrelipase capsules for the Pancrease® brand. The *in vitro* analysis on enzyme activity was investigated after the treatment failure reported. The analysis discovered that lipase activity was less than 200 units per capsule compared to 6,820 units per capsules from Pancrease® after one-hour exposure to simulated gastric fluid. These *in vitro* data indicated that the enteric-coating of the generic product was not bioequivalent to the prescribed brand drug Pancrease®. The patients' gastrointestinal symptoms and fat malabsorption rapidly resolved after the brand Pancrease® therapy was reinstituted. The authors concluded that non-bioequivalent generic products should not be used to treat patients. They also recommended that physicians should mark their prescriptions for pancreatic enzyme products "do not substitute" and that pharmacists should not substitute one brand of PEP for another without consulting the prescribing physician.

7. Nutrient Interactions: Enteric-coated pancreatic enzymes such as Ultrase® given as digestive aids can have a number of effects on the absorption of nutrients, both positive and negative. Adequate absorption of fat-soluble vitamins requires proper fat absorption, and treatment with pancreatic enzymes in combination with vitamin supplementation has

been used to improve the absorption of Vitamins A and D in CF patients. However, PEPs can form insoluble complexes with folic acid, and may, therefore, impair folate absorption. The extent of this impairment and its consequences are unknown, but may be an important consideration in women of child-bearing age since adequate folate intake during pregnancy is associated with a reduced risk of neural tube defects in infants. PEPs have been shown to contain selenium at concentrations that result in improved absorption of selenium in patients. Iron absorption, on the other hand, may be reduced by pancreatic enzyme preparations, and some authors recommend that the iron status of patients with CF should be routinely monitored, that the serum ferritin level may be the most appropriate measurements of total body iron stores, and that iron should not be administered in close proximity in time of PEPs. However, since the study that gave rise to these recommendations enrolled only young adults, the results from the study may not be applicable to growing children.[20]

9.2 Labeling Recommendations

This Reviewer recommends an approvable (AE) action; therefore, labeling was not reviewed, and will be re-visited at the time of labeling negotiations if/when the NDA is approved.

The Sponsor requested a Pediatric Deferral for children less than two years of age to allow development of an age-appropriate formulation, for which a study will be completed as a Post-Marketing Commitment (PMC) should Ultrase® be approved. Additionally, based on the Division's recommendation, the Sponsor has agreed to conduct a study of children between two and seven years of age, which result will be reflected in the labeling if the results are successful. No other clinical trials are required.

Other general comments regarding labeling recommendations are as follows:

1. The literature case reports described in Section 9.3 Literature Review should be considered.
2. Only those studies that were conducted in the TbMP should be included in the labeling (i.e., results from Studies 96-01 and 96-02 should not be included).
3. Dose recommendation should comply with the CFF/FDA dosing Guidelines.
4. The indication statement should state that Ultrase® has been shown to treat steatorrhea caused by EPI due to CF, CP, and other related disorders.
5. A brief discussion of fibrosing colonopathy and hyperuricemia/hyperuricosuria should be included. The following description of the former may be considered: Fibrosing colonopathy is a term used to describe a condition seen in patients with CF who have taken high amounts of PEP (>6,000 lipase units/kg/meal). At its most advanced stage, this condition leads to colonic strictures. Colonic strictures have been reported in CF patients treated with both high and lower-strength enzyme supplements.[21] The possibility of bowel stricture should be considered if symptoms suggestive of gastrointestinal

20 Tempsky, WT, Rosenstein, BJ, Carroll JA, et al. Effect of pancreatic enzyme supplement on iron absorption. AJDC 1989; 143: 969-972.
21 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86

obstruction occur. Since impaired fluid secretion may be a factor in the development of intestinal obstruction, care should be taken to maintain adequate hydration particularly in warm weather.[22]

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

9.4 Appendix 1: Federal Register (FR) Notice and Regulatory History of PEPs

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR): [23]

- In 1979, the Agency proposed establishing monographs for OTC PEPs.
- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, pre-clearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.
- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.
- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.
- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an application as stated in 21CFR 314.50. A draft Guidance for submitting NDAs for PEPs was also published at that time.
- In 2006, the Final Guidance for submitting NDAs for PEPs was published ("the Guidance").[24]

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22 Lands, L, Zinman, R, Wise, M, et al. Pancreatic function testing in meconium disease in CF: Two case reports. J of Ped Gastroenterol and Nutrition 1988; 7:276-279

23 This regulatory history of pancreatic enzyme products was compiled by FDA's clinical review team leader, Anne Pariser, M.D. (see Clinical Team Leader Summary Review of NDA 20-725, July 31, 2007)

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

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

9.5 Appendix 2: Listing of Individual Site Investigator and Study Sites for Study UMT20CF05-01

Principal/Coordinating Investigator:
Michael Konstan, MD (Cleveland, OH)

Individual Site Investigator:
Site 01 Gavin Graff, MD (Pennsylvania State University and the Hershey Medical Center)
Site 02 Theodore Liou, MD (University of Utah)
Site 03 Steven Strausbaugh (University Hospitals of Cleveland)
Site 05 Richard Ahrens, MD (University of Iowa)
Site 06 Katryn Moffett (West Virginia University Research Corporation)
Site 07 Samya Nasr, MD (University of Michigan)
Site 09 Susan Millard, MD (Spectrum Health Hospital)
Site 10 Jamshed Kanga (University of Kentucky Research Foundation)

9.6 Appendix 3: Summary of AEs by SOC and PT, Pivotal Study

System Organ Class		Treatment	
Preferred Term	Statistic	Ultrase® MT20	Placebo
Number of Patients in the Safety Population Who Entered the Treatment Period	N	30	31
Number of TEAEs	n	33	109
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	0	1 (3.2%)
WHITE BLOOD CELL DISORDER	n (%)	0	1 (3.2%)
GASTROINTESTINAL DISORDERS	n (%)	8 (26.7%)	19 (61.3%)
ABDOMINAL DISCOMFORT	n (%)	0	1 (3.2%)
ABDOMINAL DISTENSION	n (%)	0	1 (3.2%)
ABDOMINAL PAIN	n (%)	2 (6.7%)	12 (38.7%)
ABDOMINAL PAIN UPPER	n (%)	4 (13.3%)	6 (19.4%)
ABDOMINAL TENDERNESS	n (%)	0	2 (6.5%)
CONSTIPATION	n (%)	2 (6.7%)	2 (6.5%)
DIARRHOEA	n (%)	0	3 (9.7%)
FAECAL VOLUME INCREASED	n (%)	0	1 (3.2%)
FLATULENCE	n (%)	1 (3.3%)	5 (16.1%)
NAUSEA	n (%)	0	5 (16.1%)
STEATORRHOEA	n (%)	0	1 (3.2%)
VOMITING	n (%)	0	3 (9.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	3 (9.7%)
CHILLS	n (%)	0	1 (3.2%)
FATIGUE	n (%)	0	1 (3.2%)
GENERAL PHYSICAL HEALTH DETERIORATION	n (%)	0	1 (3.2%)
LETHARGY	n (%)	0	1 (3.2%)
PYREXIA	n (%)	0	2 (6.5%)
INVESTIGATIONS	n (%)	6 (20.0%)	12 (38.7%)
ALANINE AMINOTRANSFERASE INCREASED	n (%)	1 (3.3%)	2 (6.5%)
ASPARTATE AMINOTRANSFERASE INCREASE	n (%)	0	1 (3.2%)
BLOOD ALKALINE PHOSPHATASE INCREASED	n (%)	1 (3.3%)	0
BLOOD CALCIUM DECREASED	n (%)	0	1 (3.2%)
BLOOD GLUCOSE INCREASED	n (%)	0	2 (6.5%)
BLOOD POTASSIUM INCREASED	n (%)	0	1 (3.2%)
BLOOD TRIGLYCERIDES INCREASED	n (%)	0	1 (3.2%)
BREATH SOUNDS ABNORMAL	n (%)	0	1 (3.2%)
FAECAL FAT INCREASED	n (%)	4 (13.3%)	9 (29.0%)
FORCED EXPIRATORY VOLUME DECREASED	n (%)	1 (3.3%)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	n (%)	0	1 (3.2%)
LABORATORY TEST ABNORMAL	n (%)	3 (10.0%)	7 (22.6%)
LABORATORY TEST ABNORMALITY	n (%)	0	1 (3.2%)
NEUTROPHIL COUNT INCREASED	n (%)	0	1 (3.2%)
PULMONARY FUNCTION TEST DECREASED	n (%)	0	1 (3.2%)
WEIGHT DECREASED	n (%)	0	3 (9.7%)
METABOLISM AND NUTRITION DISORDERS	n (%)	0	2 (6.5%)
DECREASED APPETITE	n (%)	0	2 (6.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	1 (3.3%)	3 (9.7%)
ARTHRALGIA	n (%)	0	1 (3.2%)
MUSCULOSKELETAL DISCOMFORT	n (%)	0	1 (3.2%)
MYALGIA	n (%)	1 (3.3%)	1 (3.2%)
NERVOUS SYSTEM DISORDERS	n (%)	2 (6.7%)	2 (6.5%)
DIZZINESS	n (%)	0	1 (3.2%)

HEADACHE	n (%)	2 (6.7%)	1 (3.2%)
PSYCHIATRIC DISORDERS	n (%)	0	1 (3.2%)
PANIC ATTACK	n (%)	0	1 (3.2%)
	n (%)		
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	0	1 (3.2%)
DYSMENORRHOEA	n (%)	0	1 (3.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	6 (20.0%)	6 (19.4%)
COUGH	n (%)	1 (3.3%)	1 (3.2%)
DYSPHONIA	n (%)	0	1 (3.2%)
DYSPNOEA	n (%)	0	1 (3.2%)
NASAL CONGESTION	n (%)	0	1 (3.2%)
NASAL TURBINATE HYPERTROPHY	n (%)	1 (3.3%)	0
PERITONSILLAR ABSCESS	n (%)	1 (3.3%)	0
PHARYNGOLARYNGEAL PAIN	n (%)	2 (6.7%)	1 (3.2%)
PLEURITIC PAIN	n (%)	0	1 (3.2%)
PRODUCTIVE COUGH	n (%)	0	1 (3.2%)
RALES	n (%)	2 (6.7%)	2 (6.5%)
RHINORRHOEA	n (%)	1 (3.3%)	3 (9.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	n (%)	1 (3.3%)	0
RASH MACULO-PAPULAR	n (%)	1 (3.3%)	0
SURGICAL AND MEDICAL PROCEDURES	n (%)	0	1 (3.2%)
PAIN MANAGEMENT	n (%)	0	1 (3.2%)
VASCULAR DISORDERS	n (%)	2 (6.7%)	0
EPISTAXIS	n (%)	2 (6.7%)	0

Notes:

1. Adverse events have been coded using the MedDRA dictionary, version 9.0.
2. Treatment emergent adverse events (TEAEs) include all new AEs that occurred during the Treatment Periods. AEs already present at the beginning of one of these study periods that worsen in intensity following exposure to the study period medication have also been considered as treatment emergent.
3. Patients with more than one occurrence of the same preferred term/system organ class during a particular study period have been counted only once within the preferred term/system organ class of that study period.
4. Percentages based on the total number of Safety patients within each treatment group and each study period.
5. Terms 'lacrimation increased' and 'rhinitis' were removed from this derivative table as these events only occurred during the Stabilization Periods, data that are presented in the more detailed Section 14 Tables

Source: Table 14.3-2

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/s/

Joanna Ku
7/1/2008 02:05:10 PM
MEDICAL OFFICER

Anne Pariser
7/1/2008 03:06:53 PM
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