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APPLICATION NUMBER:

22-542Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	February 9, 2012
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-542
Applicant	Aptalis Pharma US, Inc.
Date of Submission	September 1, 2011
PDUFA Goal Date	March 1, 2012
Proprietary Name / Established (USAN) names	Viokace® pancrelipase
Dosage forms / Strength	Viokace® (pancrelipase) tablets for oral administration, in USP units <ul style="list-style-type: none"> ▪ Viokace 10,440 lipase/39,150 protease/39,150 amylase ▪ Viokace 20,880 lipase/78,300 protease/78,300 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy
Recommended Action:	Approval under 21 CFR 314

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1. Introduction

A Complete Response (CR) Letter was sent by the Division on November 28, 2010. This resubmission, received September 1, 2011, is a complete response to that letter, and represents the second review cycle for Viokace (pancrelipase), a non-enteric coated pancreatic enzyme product (PEP). Viokace 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. The CMC deficiencies were related to drug substance issues. The CR letter cited a letter sent to the drug substance DMF holder, and minutes of a meeting with the drug substance DMF holder and the Applicant. Facility inspection deficiencies were also included in the CR letter.

It should be noted that the Applicant name changed from Axcan Pharma US, Inc. to Aptalis Pharma US, Inc; the Division was notified of this in a letter submitted to the NDA October 13, 2011 and received October 14, 2011.

2. Background

2.1 Clinical Background

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

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

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

¹ Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *J Pediatric Gastroenterology and Nutrition*. 2002 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.

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; it should be noted that each of these PEPs are enteric-coated formulations.

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

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

Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products

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

PEP Guidance: The draft PEP guidance was published in 2004, and the final PEP Guidance was published in 2006 (Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs).

It should be noted that a Risk Evaluation and Mitigation System (REMS) was implemented at the time of approval of each of the approved PEPs (Creon, Zenpep, and Pancreaze) in

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.

order to ensure that the benefits of the drug outweighed: (1) the known risk of fibrosing colonopathy which may be mitigated by properly dosing each of the PEPs; and (2) the theoretical risk of transmission of viral disease to patients treated with a porcine-derived pancreatic enzyme product. However, after consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), the Division determined that a REMS is no longer necessary to ensure the benefits of the drug outweigh the risks described above because labeling is adequate to describe the risks. The Medication Guide will continue to be part of the approved labeling. Letters indicating that the REMS was no longer required were sent to each of the sponsors of the approved PEPs – Creon (May 9, 2011), Zenpep (June 10, 2011), and Pancreaze (June 20, 2011).

2.2.2 Regulatory History of Viokace

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

Table 2. Pertinent Regulatory History of Viokace

Date	Event
August 2000	Original IND submission*
October 2006	End of Phase 2 Meeting
December 2006	Special Protocol Assessment for Pivotal Study (VIO16EPI07-01) submitted
February 2007	Meeting with the Sponsor to further discuss pivotal study design
May 2007	Fast Track Designation granted
July 2007	Pre-NDA Meeting
April 2009	Rolling Review granted
April 2009	Modules 1, 2, and 4 of NDA 22-542 submitted
July 2009	Module 3 of NDA 22-542 submitted [#]
October 2009	Module 5 of NDA 22-542 submitted [†]
November 2010	Complete Response Action
September 2011	Class II Resubmission [‡] (current submission)
January 2012	Meetings with the Applicant and with (b) (4) to discuss methods transfer report submissions, and information needed for adequate assay transfer studies.

*IND 60716

[#]Submission also included addition of documents to Modules 1 and 2

[†]Submission also included addition of documents to Modules 1, 2, and 3

[‡] Complete Response to the Action Letter

It should be noted that Viokace was commercially available in the US until April 2010 (see Section 2.2.1); it was marketed under the name “Viokase.” The CMP formulation that was on the market from 2003 to earlier this year and the TbMP are the same formulation.

It should also be noted that Viokace if approved would be the first approved non-enteric coated pancreatic enzyme product.

2.3 Current Submission

The NDA resubmission was received on September 1, 2011. It was classified as a six-month resubmission with a PDUFA deadline of March 1, 2012.

No Advisory Committee meeting was convened to discuss this application.

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

- (1) Clinical Review of Safety Update by Marjorie Dannis, dated December 12, 2011 (NDA 22-542)
- (2) CMC Reviews from Division of Therapeutic Proteins (DTP):
 - (a) NDA Review by Richard Ledwidge dated February 1, 2012 (NDA 22-542)
 - (b) DMF Review by Richard Ledwidge dated February 1, 2012 (DMF (b) (4))
 - (c) CMC Summary Review by Emanuela Lacana dated February 9, 2012 (NDA 22-542)
- (3) Microbiology Reviews from New Drug Microbiology Staff (NDMS)
 - (a) NDA Review by Denise Miller dated February 3, 2012 (NDA 22-542)
 - (b) DMF Review by Stephen Langille dated January 31, 2012 (DMF (b) (4))
- (4) Division of Medical Policy Programs (DMPP) Review by Sharon Mills dated February 6, 2012 (NDA 22-542)
- (5) Office of Prescription Drug Promotion (OPDP) Review by Twyla Thompson and Kathleen Klemm dated February 8, 2012 (NDA 22-542)
- (6) Reviews from the Division of Medication Error Prevention and Analysis (DMEPA):
 - (a) Proprietary Name Review by Manizheh Siahpoushan dated December 5, 2011 (NDA 22-542)
 - (b) Label and Labeling Review by Manizheh Siahpoushan dated October 31, 2011 (NDA 22-542)
- (7) Study Endpoint and Labeling Development (SEALD) Labeling Review by Jeanne Delasko dated February 9, 2012 (NDA 22-542)

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

- Proprietary Name Granted Letter sent to Aptalis Pharma US, Inc. dated December 8, 2011 (signed by Carol Holquist, Director Division of Medication Error Prevention and Analysis [DMEPA])

The reviews should be consulted for more specific details of the application. The reader is also referred to the CDTL Review for the initial review cycle, dated November 24, 2010, as well as to the primary review documents from the first 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 CMC Primary Reviews by Richard Ledwidge dated February 1, 2012 (NDA 22-542 and DMF (b) (4)), the CMC Secondary Review by Emanuela Lacana dated February 9, 2012 (NDA 22-542), the Microbiology Review by Denise Miller dated February 3, 2012 (NDA 22-542), and the Microbiology Review by Stephen Langille dated January 31, 2012 (DMF (b) (4)) for complete information.

3.1 Overview

An overview of the drug substance (DS), drug substance viral issues, and drug product (DP) and packaging is provided below.

3.1.1 Overview of Drug Substance (DS)

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

(b) (4) is the DS DMF Holder for Ultresa (NDA 22-222) and Pertzye (NDA 22-175) as well as for Viokace. Thus, there is an extensive regulatory history with the DS DMF Holder because the other NDA's (for Ultresa and Pertzye) were originally submitted in July 2007 and October 2008, respectively, and there have been re-submissions of those NDA's.

The DS used in Viokace is DS 1252, (b) (4) DS 1206. The DS used in Ultresa is DS 1286, (b) (4) DS 1208. The DS used in Pertzye is DS 1206 and DS 1208.

3.1.2 Overview of DS Viral Issues

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

To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

3.1.3 Overview of Drug Product (DP) and Packaging

The DP is manufactured by Confab Laboratories; it should be noted that pertinent information related to the DP and packaging has been submitted to NDA 22-542.

The DP manufacturing process entails: (b) (4)

Viokace tablets are presented in

two strengths based on lipase activity (10,440 USP units lipase, and 20,880 USP units lipase). The bulk tablets are stored in (b) (4)

The tablets are packaged in high density polyethylene (HDPE) bottles. Each bottle contains a desiccant packet. The tablet count is 100 tablets per bottle.

3.2 Initial Review Cycle

In the initial review cycle, the Drug Substance and Drug Product reviews were conducted by Wei Guo (DMF (b) (4) and NDA 22-542), the Microbiology reviews were conducted by Stephen Langille (DMF (b) (4)) and Denise Miller (NDA 22-542), and a CMC Secondary Review was conducted by Emanuela Lacana (NDA 22-542). Each of these reviews was summarized in the CDTL review by Anil Rajpal. (Please refer to the CDTL review, and each of the individual reviews for more information.)

The CR Letter (see Appendix 2) cited a letter sent to the drug substance DMF holder, and minutes of a meeting with the drug substance DMF holder and the Applicant; it also included facility inspection deficiencies.

3.2.1 DS Viral Issues (first cycle)

Many of the DS viral issues have been addressed in the reviews of other NDA's (i.e., Ultresa and Pertzye NDA's) that used the same DS DMF (see Section 3.1.1). In the most recent review of DS viral issues (dated April 28, 2010; filed under NDA 22-222), the DS Viral Issues Reviewer (Howard Anderson) concluded that deficiencies exist, but did not preclude approval of that application since these could be addressed as postmarketing commitments (PMC's) (see CDTL Review of Ultresa NDA dated May 5, 2010 for complete information). See also Sections 3.3.1 and 13.6 of this CDTL Review.

3.2.2 DS Non-Viral Issues (first cycle)

The overall findings of the DS Non-Viral Issues reviewer were that each of the deficiencies identified in the previous cycle was adequately addressed; however, the secondary CMC reviewer identified an additional deficiency item.

The deficiency item for DS non-viral issues that was sent to (b) (4) was related to (see final wording of Item #6 in Deficiency Letter sent to (b) (4) in Appendix 3): data demonstrating no adverse impact on product quality from a change in the DS intermediate storage container from (b) (4) to (b) (4) drums.

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

3.2.3 DP Issues (first cycle)

The overall findings of the DP reviewer were that deficiencies exist, but these do not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's). (See Sections 3.3.3 and 13.6 of this CDTL Review.)

3.2.4 Microbiology Issues (first cycle)

The overall findings of the Microbiology Reviewer were that NDA 22-542 cannot be recommended for approval until the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) (see Appendix 3) have been adequately addressed.

The deficiency items for microbiology issues that were sent to (b) (4) were related to (see final wording of Items #7 to #14 in Deficiency Letter sent to (b) (4) in Appendix 3): (7) efforts to reduce the bioburden on incoming pancreas glands; (8) microbial limits specification; (9) updated manufacturing procedures including timepoints for microbiological samples; (10) microbiological monitoring of (b) (4) (11) microbiological alert and action levels; (12) commitment to clean processing equipment between batches; (13) updated microbial limits acceptance criteria for stability batches of DS; and (14) release test procedure for *Bacillus cereus*, and commitment to test each batch of DS for *Bacillus cereus* prior to release.

3.2.5 Facility Inspections (first cycle)

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

“...the levels found on inspection are considerably lower than the cutoff for causing illness (10^6 CFU/g) as per the draft guidance [*draft guidance for FDA staff entitled “Sec 527.300 Dairy Products-Microbial Contaminants and Alkaline Phosphatase Activity”*]. However, there still exists a small but potential risk with the levels that were measured. [*reference to e-mail from Dr. Benjamin Lorenz⁴ 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

⁴ Dr. Benjamin Lorenz (Clinical Reviewer in the Division of Anti-infective and Ophthalmology Products) was consulted for the issue of microbial contamination related to an earlier facility inspection; see also Consult Review by Dr. Lorenz dated June 5, 2009 filed under NDA 22-222 (Ultresa).

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.”

Confab Inspection: Based on the Establishment Evaluation System (EES) report, there is an “Acceptable” recommendation from the Office of Compliance for Confab dated January 5, 2010. The OAI Status for Confab in the Summary Report for NDA 22,542 is “None.”

^{(b) (4)} Inspection: Based on the Establishment Evaluation System (EES) report, there is an “Acceptable” recommendation from the Office of Compliance for ^{(b) (4)} (contract testing laboratory) dated July 16, 2010. The OAI Status for ^{(b) (4)} in the Summary Report for NDA 22,542 is “None.”

^{(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 22,542 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 22,542 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 22,542 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 22,542 is “None.”

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

The Office of Compliance ^{(b) (4)}

3.3 Current Review Cycle

In the current review cycle, the Drug Product and Drug Substance reviews were conducted by Richard Ledwidge (DMF ^{(b) (4)} and NDA 22-542), and the Microbiology reviews were conducted by Stephen Langille (DMF ^{(b) (4)}) and Denise Miller (NDA 22-542). A CMC Secondary review was conducted by Emanuela Lacana (NDA 22-542).

3.3.1 DS Viral Issues (Current Cycle)

A separate DS Viral Issues Review was not conducted during the current review cycle. The DS viral issues deficiencies identified in a prior review (see Section 3.2.1) were deemed to

^{(b) (4)}

not preclude approval of the application since these could be addressed as postmarketing commitments (PMC's).

DS Viral Postmarketing Commitments (PMC's):

DS viral items to be communicated to (b) (4) (taken from Dr. Lacana's review) as postmarketing commitments (PMC's) are provided below. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

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

3.3.2 DS Non-Viral Issues (Current Cycle)

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

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

DS Non-Viral Postmarketing Commitments (PMC):

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

DS PMC #8: To provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality. Final report submitted [Insert date]

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

A summary of the DS reviewer's assessment of the adequacy of (b) (4) response to each of the parts (a-d) of Item #6 in the letter to (b) (4) (see Appendix 3) is presented below:

- (6a) Extractable/leachable studies and risk analysis on (b) (4) container: The DS Reviewer concluded that the extractable/leachable studies conducted were appropriate, and that the two compounds that were found (b) (4) posed a negligible safety risk; however, (b) (4) switched to (b) (4) containers based on the extractable/leachable results. The DS Reviewer concluded that a leachable study that looks for metal analysis by ICP-MS should be conducted, and that this issue may be addressed as a PMC (see DS PMC #8 above.)
- (6b-c) Quality and stability data of pancrelipase manufactured using the (b) (4) container: The DS Reviewer concluded that the release tests are within specifications but noted that a thorough characterization (i.e., impurity testing) was not performed; the DS Reviewer added that this is not considered a deficiency as (b) (4) has switched to (b) (4) containers. Regarding stability data in (b) (4), the DS Reviewer commented that enzyme activities and microbial counts are unaltered over 12 months.
- (6d) Cleaning validation studies supporting re-use of (b) (4) containers: The DS Reviewer concluded that no visible pancrelipase API remains between runs and that total organic carbon and microbiological samples were well below specified limits.

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

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

- Quality and stability data of pancrelipase manufactured using (b) (4) containers: The DS Reviewer concluded that although a thorough characterization

(e.g., impurity testing) was not performed, the stability study supports the notion that storage in the (b) (4) drums does not negatively impact product quality attributes. The DS Reviewer commented that enzyme activities and microbial counts were unchanged during a (b) (4) storage in the (b) (4) containers, noting that this is longer than the allowed holding time of (b) (4). The DS Reviewer also commented that all specifications were met in four CoA's from lots manufactured using the (b) (4) containers.

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

3.3.3 DP Issues (Current Cycle)

The DP Reviewer noted that deficiencies exist, but do not preclude approval of the application since these can be addressed as PMC's; it should be noted that the DP reviewer in the previous review cycle also concluded that DP deficiencies could be addressed as PMC's.

PMC's recommended by the DP reviewer are provided below; this is followed by a summary of the DP reviewer's assessment of the response from Aptalis and (b) (4) to a deficiency item identified in the previous review cycle, and the DS reviewer's assessment of additional pertinent information provided by the Applicant.

DP Postmarketing Commitments (PMC's):

DP items to be communicated to (b) (4) (taken from Dr. Lacana's review) as PMC's are provided below. (The numbering of the PMC's corresponds to the list of PMC's in Section 13.6 of this CDTL Review.)

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

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

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

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

Below is a summary of the DP Reviewer's assessment of the response from Aptalis and (b) (4) addressing the issue of Bacillus cereus Enterotoxin (BCE) presence in pancrelipase API (see Item #14 in the Letter to (b) (4); Appendix 3). See also Section 3.3.4 of this CDTL Review.

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

another assay that is not subject to interferences in the pancrelipase API is required to detect BDE.

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

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

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

The DP reviewer noted that the typical BDE concentration in the late log phase of a *Bacillus cereus* culture is (b) (4) ng/mL, and that during (b) (4). Thus, the DP Reviewer concluded that the studies demonstrate that any pre-formed BDE will be rapidly degraded during the manufacturing of pancrelipase API. The DP Reviewer commented that the results of the studies using Western Blot Methods are consistent with the scientific literature, and that the risk of pre-formed BDE being administered to patients is negligible.

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

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

In process limits were set as follows:

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

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

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

Additional Pertinent Information (Assay Transfer):

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

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

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

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

The DP Reviewer offered the following recommendations:

- While the transferred assays have been validated for linearity, specificity etc., a robust assay transfer study should also include different test samples to confirm the validation characteristics the assays are purported to possess.
- The Applicant should provide data on multiple lots of drug product to allow for a wider range of product characteristics and an analysis of the results demonstrating equivalency between the two sites using appropriate statistical methodology (equivalency testing) with defined confidence intervals.
- The method transfer exercise should include justifications of acceptance criteria and sample sizes.

The Agency discussed the inadequacy of the Applicant's submitted method transfer exercise and a regulatory path forward for NDA 22542 in a teleconference that took place on January 30, 2012. The Applicant provided further clarification and a revised proposal.

Further Clarification: Aptalis clarified that for NDA 22-542 drug product release testing is primarily performed at Confab Laboratories, Inc. in Quebec Canada and that (b) (4) would be used as an alternate site.

Revised Proposal: Aptalis proposed removing (b) (4) from the list of manufacturers for NDA 22542 (for drug product release testing) until a robust assay transfer exercise is conducted and reviewed by the agency.

Overall Recommendation: The DP Reviewer concluded that Aptalis' proposal above is acceptable.

Applicant's Response: The Applicant sent a letter on February 1, 2012, received February 2, 2012, stating that (b) (4) will be removed as an alternate site for drug product release testing. (It should be noted that microbial testing will remain at (b) (4).)

3.3.4 Microbiology Issues (Current Cycle)

The Microbiology Reviewers deemed the responses to each of the deficiency items in the letter sent to (b) (4) October 27, 2010 satisfactory. See Microbiology Reviews by Stephen Langille dated January 31, 2012 (DMF (b) (4)) and by Denise Miller (NDA 22-542) for complete information.

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

A summary of Dr. Langille's assessment of the adequacy of (b) (4) response to Items #7 through #13 in the Letter to (b) (4) dated October 27, 2010 (see Appendix 3) is presented below.

- (7) Efforts to reduce the bioburden on incoming pancreas glands: (b) (4) received written confirmation from their slaughterhouses that the time between pancreas harvesting and (b) (4) will be reduced to no more than (b) (4). The Microbiology Reviewer deemed the response to this item satisfactory, and commented that the hold times will be confirmed during slaughterhouse audits and technical visits.
- (8) Microbial limits specification: Microbiological specifications for the 1206 and 1208 manufacturing processes provided by (b) (4) were deemed satisfactory by the Microbiology Reviewer. One of the specifications was that TAMC must be no more than (b) (4) CFU/g.
- (9) Updated manufacturing procedures including timepoints for microbiological samples: The time limits and steps at which microbiological samples were to be collected were provided by (b) (4) for the 1206 and 1208 processes. (b) (4) response to this item was deemed satisfactory by the Microbiology Reviewer.
- (10) Microbiological monitoring of (b) (4): The bioburden alert and action levels from the (b) (4) manufactured using the 1206 and 1208 processes were provided by (b) (4) and deemed satisfactory by the Microbiology Reviewer. (b) (4) also reiterated their commitment to test the bioburden of the (b) (4) from each drum immediately prior to (b) (4).
- (11) Microbiological alert and action levels: The action level provided by (b) (4) of no more than (b) (4) CFU/g for the (b) (4) samples was deemed satisfactory by the Microbiology Reviewer.

- (12) Commitment to clean processing equipment between batches: (b) (4) reiterated their commitment to clean all processing equipment between each batch with the exception of the (b) (4) and (b) (4); this response was deemed satisfactory by the Microbiology Reviewer.
- (13) Updated microbial limits acceptance criteria for stability batches of DS: The Microbiology Reviewer noted that the current acceptance criteria for all stability samples are (b) (4) CFU TAMC/g, and stated that the response to this item is acceptable.

It should be noted that the Response to Item 14 in the Letter to (b) (4) (release test procedure for *Bacillus cereus*, and commitment to test each batch of DS for *Bacillus cereus* prior to release) was reviewed by the DP Reviewer (see Section 3.3.3 of this CDTL Review).

3.3.5 Facility Inspections (Current Cycle)

Recommendations from the Office of Compliance (based on the Establishment Evaluation System (EES) report) are that all facilities for NDA 22-542 have an “acceptable” status in EES.⁷

The facilities (as per a listing in the Addendum to the 356h form in Module 1 of the submission received February 6, 2012) are the following:

- (b) (4) (DMF (b) (4))
- Confab Laboratories Inc. (St-Hubert, Québec, Canada)
- (b) (4)

3.4 Final Recommendation

An Approval Action is the final recommendation by CMC.

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

4. Nonclinical Pharmacology/Toxicology

4.1 Initial Review Cycle

Nonclinical pharmacology/toxicology data were reviewed by the Primary Nonclinical Pharmacology/Toxicology reviewer, Niraj Mehta, and Secondary Nonclinical Pharmacology/Toxicology reviewer, David Joseph, and summarized in the CDTL review by Anil Rajpal. (Please refer to each of those reviews for more information.)

⁷ Recommendations from the Office of Compliance are based on an email from Zhong Li (Chemist, Office of Compliance / Office of Manufacturing and Product Quality / Division of Good Manufacturing Practice Assessment / New Drug Manufacturing Assessment Branch) dated February 3, 2012.

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance⁸, 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 Viokace clinical development program. However, toxicology studies are needed if the excipients in the Viokace 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 Viokace 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 Viokace.

The non-clinical information provided by the Applicant in the submission was mostly related to the excipients (colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, stearic acid, microcrystalline cellulose, and talc) 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 Viokace, and from information from the FDA Inactive Ingredients Database.

The overall conclusion from Dr. Mehta and Dr. Joseph 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 that could result from Viokace administration, and that an approval of the Viokace NDA is recommended.

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

- **Indications and Usage section of Highlights:** (b) (4) should be changed to “VIOKACE is a combination of porcine-derived lipases, proteases, and amylases.”
- **Use in Specific Populations section (Pregnancy subsection):** Wording should be revised to:
“Teratogenic Effects
Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The risks and benefits of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes. (b) (4)
”

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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf>> April 2006.

- Use in Specific Populations section (Nursing Mothers subsection): Wording should be revised to:
“It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIOKACE is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.”
- 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.”

Dr. Mehta and Dr. Joseph also noted in their reviews that since Viokace administration may result in a substantial intake of lactose monohydrate (up to (b) (4)/day in a 60-kg patient), there appears to be a potential for adverse reactions in lactose intolerant patients. Dr. Mehta noted the following in his review: “Approximately 10-20% of lactose-intolerant individuals, in two studies, showed clinical symptoms of intolerance after ingestion of 3-5 g of lactose (Bedine et al, Gastroenterology, 65, pg. 735-743, 1973; Gundmand-Hoyer E, Am J Dig Dis, 22(3), pg. 177-181, 1977). Given the daily intake of lactose that occurs with the daily consumption of dairy products as recommended by the USDA, the estimated maximum dose of lactose monohydrate resulting from administration of VIOKACE® is not considered to be a safety concern for patients who tolerate lactose.” This issue was discussed internally in meetings that included Dr. Mehta and Dr. Joseph after their reviews had been written. Based on those discussions, there is an addition to the Warnings and Precautions section of a subsection titled “Potential for Exacerbation of Symptoms of Lactose Intolerance” that has the following wording: “VIOKACE tablets contain lactose monohydrate. Patients who have lactose intolerance may not be able to tolerate VIOKACE.”

4.2 Current Review Cycle

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

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

4.3 Final Recommendation

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

5. Clinical Pharmacology/Biopharmaceutics

5.1 Initial Review Cycle

Clinical pharmacology data were reviewed by the Clinical Pharmacology reviewer, Lanyan Fang, and summarized in the CDTL review by Anil Rajpal. (Please refer to each of those reviews for more information.)

The Applicant conducted an *in vivo* intubation study (bioavailability study; VIO16IP07-01). This was reviewed by Dr. Fang and her conclusions are described below:

This was a single-dose, open-label, crossover study to evaluate the intraduodenal delivery of Viokace (20,880 lipase units tablet) in 14 patients with EPI due to chronic pancreatitis. Patients were randomized to receive three tablets of Viokace (20,880 lipase units tablet) with or without Ensure Plus. Duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Twelve patients were in the per-protocol population. The cumulative activity of lipase ($p=0.0034$), trypsin ($p=0.0017$), and amylase ($p=0.0188$) recovered during the 2-hour perfusion/aspiration was statistically significantly greater after administration of Ensure Plus with Viokace as compared to administration of Ensure Plus alone. The clinical pharmacology reviewer provided a summary of the enzyme activity ratios and the percent recovery (see table below).

Table 3. Summary of Total Enzyme Activity Ratio and Percent Recovery

Effect	Ratio (Based on Observed Values)	% Recovery
Total Lipase Activity	1.91	64.1%
Total Trypsin Activity	4.80	29.2%
Total Amylase Activity	2.91	21.3%

Ratios: Total amount accumulated over 2-hour period of *Ensure Plus*[®] + VIOKASE[®]16/*Ensure Plus*[®] alone

% Recovery: Percentage of enzyme recovered during 2-hour period compared to amount administered

The clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum because of many challenges in the study design, study conduct, and assay methodology. The bioavailability study is not a required study for the NDA approval.

The reader is also referred to the Biopharmaceutics Review by Albert Chen dated September 28, 2010 and addendum dated October 12, 2010. The Biopharmaceutics reviewer found the proposed dissolution methodology and specifications acceptable. The biowaiver for the lower strength (Viokace 10,440 units of lipase) was granted.

5.2 Second Review Cycle

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

5.3 Final Recommendation

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

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

7.1 Initial Review Cycle

The reader is referred to the CDTL Review by Anil Rajpal dated November 24, 2010, the Clinical Review by Marjorie Dannis dated November 10, 2010, and the Statistical Review by Shahla Farr dated November 3, 2010, for complete information.

The pivotal study (VIO16EPI07-01) was reviewed in depth by the Clinical Reviewer.

This was a multi-center, randomized, double-blind, placebo-controlled, parallel study in 50 patients, ages 24 to 70 years, with a confirmed diagnosis of EPI and CP or pancreatectomy.

Pertinent features of the study design are summarized in the table below.

Table 4. Pertinent Features of Study Design (VIO16EPI07-01)

Period	Treatment*
Screening Phase (up to 10 days)	Usual PEP [#]
Washout Phase (6 to 7 days)	• Outpatient (2 days) • Inpatient (4 to 5 days) [†] No PEP treatment
Randomization Phase (up to 10 days)	Usual PEP [#]
Treatment Phase (6 to 7 days)	• Outpatient (2 days) • Inpatient (4 to 5 days) [†] Viokace or Placebo

* Patients are on a PPI throughout the study. At screening, patients already on a PPI will continue to use the same PPI whereas patients not already on PPI will start omeprazole.

[#] Patients continue their current PEP during the screening period.

[†] 72-hour stool collection during the inpatient periods of the washout phase and the treatment phase

Viokace 20,880 lipase units tablets were administered in the study

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

The dose of Viokace during the treatment phase was 125,280 lipase units per meal (3 meals) and 41,760 lipase units per snack (2 snacks). The total daily dose was 459,360 lipase units/day. This corresponds to 7,656 lipase units/kg/day for a 60 kg person.

Patients received a proton pump inhibitor throughout the study. Patients were maintained on a controlled high fat diet of 100 grams fat per day during the inpatient periods of the washout and treatment phases.

Patients with CFA <80% in the Washout Phase were randomized to Viokace or placebo for six to seven days of treatment.

The primary efficacy endpoint was the coefficient of fat absorption (CFA) during the treatment phase. CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet. The formula for Coefficient of Fat Absorption (CFA) is provided below:

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

Of the 218 patients who enrolled, 50 entered the treatment phase, and 49 completed the study. (One patient in Viokace group discontinued after randomization because of a failure of inclusion/exclusion criteria.) Of the 168 patients who failed screening, the majority (88 patients) had clinically-documented chronic pancreatitis and steatorrhea but did not meet the criterion for fecal elastase-1 (FE-1 < 100 µg/g stool); an additional 50 clinically documented patients who met the FE-1 criterion did not have a sufficiently low Washout Phase CFA (CFA < 80%) for randomization into the treatment phase.

The demographics and selected baseline characteristics of the study are summarized in the table below.

Table 5. Demographics of Study (VIO16EPI07-01)

	Viokace (n=30)	Placebo (n=20)
Age (years)		
Mean (SD)	51 (9.9)	51 (7.6)
Min, Max	24, 70	37, 63
Gender, n(%)		
Male	22 (73%)	19 (95%)
Female	8 (27%)	1 (5%)
Race, n(%)		
White	29 (97%)	19 (95%)
Black	1 (3%)	0
Other		1 (5%)
Pancreatectomy Status		
No Pancreatectomy History	18 (60%)	10 (50%)
Post-Pancreatectomy	12 (40%)	10 (50%)

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

CFA in the washout phase, CFA in the treatment phase, and change in CFA are summarized in the table below.

Table 6. Washout Phase CFA, Treatment Phase CFA, and Change in CFA (VIO16EPI07-01)

Parameter Phase / Analysis Type	Statistic	Treatment Group	
		Viokase [®] 16 (N=30)	Placebo (N=20)
CFA%			
Wash-Out Phase	n	30	20
	Mean	47.56	56.64
	SD	24.112	22.192
	Median	53.96	63.02
	Min., Max.	-29.1, 74.5	-9.5, 93.3
Treatment Phase / PI Using the 50th Percentile			
	n	30	20
	Mean	85.52	58.02
	SD	8.902	24.249
	Median	88.34	64.87
	Min., Max.	52.6, 95.5	3.5, 93.0
	LSMean (SE)	87.8 (2.6)	58.4 (3.2)
	p-value [a]	<0.0001**	
Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile			
	n	30	20
	Mean	37.95	1.37
	SD	25.409	13.330
	Median	35.69	-1.65
	Min., Max.	1.6, 119.8	-21.4, 30.5
Percent Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile			
	n	30	20
	Mean	616.83	-5.78
	SD	2940.244	43.813
	Median	60.59	-2.79
	Min., Max.	-411.5, 16162.5	-136.6, 90.4

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

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase CFA% value as covariate

Notes:

1. LS Mean= Least Square Mean; PI= Percentile Imputation; SE= Standard Error.
2. Coefficient of Fat Absorption (CFA%) is defined as: $\{[\text{Total fat intake during the stool collection period (g)} - \text{Total fat excretion during the stool collection period (g)}] / \text{Total fat intake during the stool collection period (g)}\} \times 100\%$.

Taken from Clinical Review by Marjorie Dannis (Source: VIO16EPI107-01 Study Report (Page 91))

At baseline (i.e., during the washout period), CFA was similar in both the Viokace and placebo groups. During the treatment phase, the mean CFA for patients receiving Creon was 85.5%; the mean CFA for patients receiving placebo was 58.0%. The difference in CFA was 27.5% (p<0.0001; 95% CI: 17.8%, 37.2%). The FDA Statistician confirmed the results and was in agreement with the Applicant.

The clinical reviewer performed a subgroup analysis based on washout phase CFA. In the subgroup of patients with washout phase CFA $\leq 40\%$, the mean change in CFA was 65% in patients administered Viokace (n=10), and 4% in patients administered placebo (n=4). In the subgroup of patients with washout phase CFA $> 40\%$, the mean change in CFA was 25% in patients administered Viokace (n=20), and 1% in patients administered placebo (n=16). The clinical reviewer commented that the results suggest that patients with a washout CFA $\leq 40\%$ had a greater response to Viokace treatment than those with higher baseline CFA values.

The clinical reviewer also performed a subgroup analysis based on pancreatectomy status. In the subgroup of patients with a history of pancreatectomy, the mean treatment phase CFA was 86% in patients administered Viokace (n=12), and 64% in patients administered placebo (n=10). In the subgroup of patients with no history of pancreatectomy, the mean treatment phase CFA was 85% in patients administered Viokace (n=18), and 52% in patients administered placebo (n=10). The clinical reviewer commented that the greater difference in CFA observed in the subgroup with a history of pancreatectomy may be due to a lower washout phase CFA in that subgroup compared to the subgroup with no history of pancreatectomy.

The statistical reviewer conducted an analysis of the change in CFA from the washout phase by gender (see table below).

Table 7. Analysis of Change in CFA by Gender - Mean (SD)

Gender	Change in CFA Mean (SD)		Difference (95% CI)
	Viokace	Placebo	
Female (n=9)	63.0 (33.5) (n=8)	-19.0 (0) (n=1)	82.0 (-1.9, 166.0)
Male (n=41)	28.8 (13.9) (n=22)	2.4 (12.8) (n=19)	26.4 (17.9, 34.9)

(Table above is taken from the Statistical Review by Shahla Farr.)

The statistical reviewer commented that there was a significant treatment by gender interaction effect ($p < 0.001$). The statistical reviewer pointed out that the small sample size for females precludes interpretation of a possible difference in gender effects.

The statistical reviewer also conducted an analysis of the change in CFA from the washout phase by age (see table below).

Table 8. Analysis of Change in CFA by Age Category - Mean (SD)

Age Category	Change in CFA Mean (SD)		Difference (95% CI)
	Viokace	Placebo	
≤ 50 Years (n=25)	44.6 (30.7) (n=14)	6.1 (14.2) (n=11)	38.5 (17.7, 59.3)
> 50 Years (n=25)	32.1 (18.8) (n=16)	-4.4 (9.9) (n=9)	36.6 (22.5, 50.6)

(Table above is taken from the Statistical Review by Shahla Farr.)

The statistical reviewer noted that there was no treatment by age interaction. The results appeared similar by age category (≤ 50 years old vs. < 50 years old).

The Clinical Reviewer commented that there were too few non-Caucasian patients to assess the results by race.

7.2 Current Review Cycle

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

7.3 Final Recommendation

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

8. Safety

The reader is referred to the CDTL Review by Anil Rajpal dated November 24, 2010, the Clinical Review by Marjorie Dannis dated November 10, 2010, and the Safety Update Review by Marjorie Dannis dated December 12, 2011 for complete information.

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

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

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

- Fibrosing Colonopathy: FC is a rare but serious condition that may result in colonic stricture. Most of the cases of FC have been reported in younger children with CF. Although the etiology of FC is not known with certainty, FC has been associated with high dose exposure to PEPs. Consensus guidelines have been established by the Cystic Fibrosis Foundation (CFF) in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.^{9,10,11} (See also Appendix 1.) Continued monitoring for fibrosing

⁹ 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.

colonopathy that is associated with PEP use is likely to best be performed through global safety surveillance.

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

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.
- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g., pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.
- Irritation to Oral Mucosa: Disruption of the protective enteric coating, and early release of the enzymes may lead to the irritation of the oral mucosa as well as loss of enzyme activity.

The theoretical risk of viral transmission is summarized below:

- Theoretical Risk of Viral Transmission: There is a concern that because PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.^{12,13} (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 Anil Rajpal dated November 24, 2010, and the Clinical Review by Marjorie Dannis dated November 10, 2010, for complete information.

In the initial review cycle, the AE profile of Viokace 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

¹⁰ 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.

¹¹ 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.

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

¹³ Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

gastrointestinal (GI) system. There were no new or noteworthy AEs noted during the initial cycle of safety review.

8.2 Current Review Cycle

The reader is referred to the Clinical Review of Safety Update by Marjorie Dannis, dated December 12, 2011 for complete information.

Dr. Dannis concluded in the Safety Update Review that the limited safety information submitted appears to be consistent with the known adverse event profile of PEPs. The Applicant provided safety information from post-marketing experience and from the clinical study update.

Postmarketing Experience: Dr. Dannis notes that based on US unit sales of Viokase during the reporting period (February 1, 2010, to June 30, 2011), patient exposure was estimated to be approximately 260,500 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 four meals per day, and patients would have an average weight of 60 kg (average weight for adult males and females).

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

- The first serious case was the occurrence of hallucinations in a 77 year old female who was started on Viokase during hospitalization for pancreatitis. The primary clinical reviewer noted that the report has not been medically confirmed. The primary clinical reviewer also noted that this patient was taking an unspecified sleep medication, and that this patient had a history of ulcerative colitis. Viokase was discontinued three to four days after it was started; the patient was placed on a low fat diet and no other pancreatic enzyme therapy was prescribed. The hallucination resolved. The primary clinical reviewer noted that the Applicant's literature and safety database search showed no similar cases, and that the Applicant concluded that there is no reasonable possibility for a causal relationship between Viokase and hallucinations.
- The second serious case was the occurrence of commensal bacteria induced necrotizing pancreatitis, gallstone pancreatitis, pleural effusion and elevated alanine aminotransferase / alkaline phosphatase levels in a 68-year-old male. The patient's medical history included hypertension, atrial fibrillation, gout, chronic kidney disease and dyslipidemia. There was no history of alcohol or tobacco use. Co-suspected medications included warfarin, amlodipine and atenolol. The primary clinical reviewer noted that the diagnosis was medically confirmed, that the patient was treated with penicillin and trimethoprim/sulfamethoxazole for the organisms identified, that the patient underwent surgery after 4 weeks, and returned to his usual state of health 2 weeks after discharge from a rehabilitation facility. Although the start date of pancrelipase relative to the onset date of the event is not known, it is likely that the patient had been prescribed pancrelipase for the gallstone pancreatitis as per the Applicant. For this reason, and

because of the absence of biological plausibility, there is no reasonable possibility for a causal relationship between pancrelipase and any of the AEs in this case.

There were a total of 25 AEs with Viokace. Other than the AE described in the serious case with Viokace above, these included two occurrences of nausea, vomiting, and diarrhea, and single occurrences of the following AEs: eye irritation, abdominal discomfort, lip exfoliation, esophageal discomfort, oral discomfort, oral pain, retching, asthenia, aggravated concomitant disease, malaise, peripheral edema, decreased therapeutic response, hypersensitivity, accidental exposure, trismus, burning sensation, oropharyngeal pain, and pruritic rash.

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: There have been no clinical studies, completed or ongoing, since the original NDA submission in October 2009.

Literature Update: The Applicant conducted a search of the medical literature for the period from February 1, 2010, to June 31, 2011. A proof-of-concept study was conducted in 42 CF patients ages 10 to 36 years to explain the reason of failure of pancreatic enzymes treatment to completely correct malabsorption and gastrointestinal symptoms in CF patients.¹⁴ Capsule endoscopy was used in 28 patients with pancreatic insufficiency (PI) and 13 patients that were pancreatic sufficient (PS); a high prevalence of small bowel injury in CF patients was observed (both in patients with PI and in patients who were PS). The study suggested a condition compatible with a “CF-bowel” that may explain the persistence of malabsorption and gastrointestinal symptoms in CF patients.

8.3 Final Recommendation

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

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

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

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

10. Pediatrics

10.1 Initial Review Cycle

10.1.1 Pediatric Research Committee (PeRC)

A Pediatric Research Committee (PeRC) meeting occurred on July 7, 2010. The PeRC agreed with the Division and the PMHS that pediatric studies for Viokace should be fully waived. The PeRC noted that PMHS should advise the Division on appropriate pediatric labeling text for this NDA.

10.1.2 Consult with Pediatric and Maternal Health Staff (PMHS)

The Pediatric and Maternal Health Staff (PMHS) was consulted prior to the PeRC meeting. The PMHS Consult Review recommended that pediatric studies for Viokace should be fully waived because the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and because the drug is not likely to be used in a substantial number of pediatric patients. (See Consult Review by Elizabeth Durmowicz dated February 16, 2010 for complete information.)

Dr. Durmowicz also provided labeling recommendations (see Consult Review by Elizabeth Durmowicz dated August 17, 2010 for complete information.). The currently proposed labeling language that was agreed upon in labeling meetings that included Dr. Durmowicz for the “Use in Specific Populations” section of Highlights and for the “Use in Specific Populations” section (“Pediatric Use” subsection) of the FPI is shown below:

- “Use in Specific Populations” section of Highlights:
 - “Pediatric Patients
 - The safety and effectiveness of VIOKACE have not been established in pediatric patients. (8.4)
 - VIOKACE use in pediatric patients may result in suboptimal growth due to tablet degradation in the gastric environment. (8.4)

- “Use in Specific Populations” section (“Pediatric Use” subsection) of FPI:
 - “8.4 Pediatric Use
 - The safety and effectiveness of VIOKACE in pediatric patients have not been established. Delayed-release (enteric-coated) capsules (b) (4) for pediatric patients. Due to greater degradation in the gastric environment, VIOKACE, a non-enteric-coated, pancreatic enzyme replacement product, may have decreased bioavailability and therefore may be less efficacious than enteric-coated formulations.^{7,8} Thus, use of VIOKACE in pediatric patients may increase the risk of inadequate treatment of pancreatic insufficiency and result in suboptimal weight gain, malnutrition and/or need for larger doses of pancreatic enzyme replacement [See Warnings and Precautions (5.1)] The efficacy of VIOKACE was established in adult patients with concomitant proton pump inhibitor (PPI) therapy. The long-term safety of PPI use in pediatric patients has not been established.”

10.2 Current Review Cycle

In the current review cycle, it was determined that it would not be necessary to present the application again to the Pediatric Research Committee (PeRC). The recommendations for labeling revisions from the previous review cycle were negotiated with the Applicant during the current 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. Viokace is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

In the initial review cycle, DSI inspections of two clinical sites of the Pivotal Study (VIO16EPI07-01) were performed; these were Site 35 (Dr. Rydewska; Warsaw, Poland; n=8) and Site 42 (Dr. Toskes; Gainesville, Florida; n=6). These sites were selected by the Division based on the number of patients enrolled (Site 35 was the largest international site; Site 42 was the largest domestic site).

Site 35:

The DSI Inspector commented that for Site 35, review of the records revealed no significant discrepancies/regulatory violations.

Site 42:

Site 42 was initially given a classification of “OAI” (Official Action Indicated) by the field investigator because four out of six patients used prohibited concomitant medications (Methadone in Subject 4205, Duragesic Patch in Subject 4201, Oscal [Calcium Carbonate] in Subject 4206, and Calcitrate in Subject 4210). The site was reclassified as “VAI” (Voluntary Action Indicated); the reason for the reclassification to VAI as per the DSI Reviewer (Dr. Malek) was that the identified issues were not considered important enough to impact data integrity. The DSI Reviewer stated in the review “The data are considered reliable in support of the application; however, the review division may choose to consider the clinical impact, if any, of the use of concomitant medications at Dr. Toskes’ site in their assessment of the application.”

The Clinical Reviewer agreed with the DSI Reviewer that the data obtained from these particular patients may be used in support of this application. The Clinical Reviewer stated that the effect on CFA results was minimal from allowing prohibited concomitant medications. Both the patients using narcotics (the patient using methadone and the patient using the Duragesic Patch) were using these medications chronically. In addition, the doses of each of the narcotics were relatively low; the Duragesic Patch dose was 50 µg/hr and the daily methadone dose was 30 mg. Regarding the patient using Oscal, the Clinical Reviewer believes that CFA results were not likely to have been affected because the dose (1 gram daily) was considerably lower than the dose described by Saunders et al. as having an effect on fat excretion; that report describes an increase of fat excretion from a daily dose of 6 grams of calcium carbonate and appears to be the basis for the exclusion of calcium carbonate in the protocol (see Primary Clinical Review from the first review cycle dated

November 10, 2010). Finally, review of the CFA results (for each of the patients that used prohibited concomitant medications) revealed that the results are similar to those of other patients in the same treatment group with similar baseline CFA values (see Tables 7, 9, and 10 in Section 5.3.1.11.6.2 of the Primary Clinical Review from the first review cycle); this further supports the conclusion that the effect on CFA results are minimal from the use of prohibited concomitant medications.

The final recommendation is that the data generated by the clinical sites of Drs. Rydewska and Toskes and appear acceptable in support of the application.

11.3 Drug Shortage

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

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

12. Labeling

12.1 Proprietary name

12.1.1 Initial Review Cycle

A review of the trade name “Viokace” was performed by Irene Chen in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Tradename Review dated January 22, 2010). DMEPA’s evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Viokace conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. The DMEPA reviewer noted that search of the FDA AERS database was conducted and identified one case where the name Viokase was identified as a cause for error; the case specified the suffix “8” in the name “Viokase 8” as the cause for error. The DMEPA Reviewer stated that because the Applicant has submitted a new name, Viokace, which does not contain a suffix, DMEPA does not believe this case is relevant to their review.

It should be noted that a previously proposed proprietary name for this product, “Viokase” was found to be unacceptable (b) (4)

A Label and Labeling Review was also performed by Irene Chen in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated October 18, 2010). Using Failure Mode and Effects Analysis and lessons learned from post-marketing experience with the pancrelipase products, DMEPA evaluated the container labels, carton labeling and insert labeling. DMEPA's findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. Detailed reasons and recommendations are provided in the DMEPA Label and Labeling Review. These recommendations were communicated to the Applicant in the CR Letter (see Appendix 2).

12.1.2 Current Review Cycle

In the current review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of "Viokace" was acceptable. See DMEPA Proprietary Name Review (dated December 5, 2011) by Manizheh Siahpoushan and Proprietary Name Granted Letter dated December 8, 2011.

The reviewer concluded that based on a standard set of databases and information sources to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review, the proposed name Viokace is acceptable from a safety perspective.

A Label and Labeling Review was also performed by Manizheh Siahpoushan in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated October 31, 2011). The DMEPA review discusses the Applicant's response to the recommendations communicated in the CR Letter as well as additional recommendations. The recommendations for labeling revisions were negotiated with the Applicant during the current review cycle.

12.2 Office of Prescription Drug Promotion Comments

The Office of Prescription Drug Promotion Comments (OPDP) [formerly the Division of Drug Marketing, Advertising and Communications (DDMAC)] found the proposed proprietary name acceptable from a promotional perspective; this is documented in the Proprietary Name review by Manizheh Siahpoushan dated December 5, 2011.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The Applicant was requested to revise the label and medication guide to be consistent with the corresponding sections for the other drugs in the class that were recently approved (Creon, Zenpep, and Pancreaze). In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from

the DMEPA Label and Labeling Review, the DMPP Patient Labeling Review, the DTP Carton and Container Label Review, the OPDP Labeling Review, and the SEALD Labeling Review. The reader is referred to each of these reviews for complete information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

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

13.2 Risk Benefit Assessment

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

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

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

13.4 Recommendation for Postmarketing Required Pediatric Studies

No postmarketing required pediatric studies are recommended for this Application.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

A PMR study is recommended, with the following language for the Approval Letter:

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risk of transmission of viral disease to patients.

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

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

1. An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients with chronic pancreatitis or history of pancreatectomy taking Viokace (pancrelipase) Tablets compared with an appropriate control group.

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

Final Protocol Submission: by [insert date]

Study Completion Date: by [insert date]

Final Report Submission: by [insert date]

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

Drug Product:

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

Drug Substance:

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

- (4) To perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy will then be implemented. Final report submitted [Insert date]
- (5) To improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PTV, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria will be submitted to the Agency. Final report submitted [Insert date]
- (6) To assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality. Final report submitted [Insert date]
- (7) To revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented. Final report submitted [Insert date]
- (8) To provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality. Final report submitted [Insert date]

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995¹⁵) 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. 2002¹⁶ 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. 1997¹⁷ 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

¹⁵ 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.

¹⁶ 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.

¹⁷ 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: NDA Deficiency Items – First Action

Deficiencies from the CR Letter (NDA 22-542) dated November 28, 2010 are provided below:

PRODUCT QUALITY

1. (b) (4) DMF (b) (4) has been reviewed in support of NDA 022542 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). (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

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

LABELING

3. Please submit draft labeling revised as follows:

A. Package Insert

- i. Per the insert labeling, you have proposed imprinting the (b) (4) on the 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease strength tablets. However, we note that (b) (4). We recommend that you remove the imprinted (b) (4) replace it with an imprint code.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

4. Please submit draft carton and container labeling revised as follows:
 - A. RETAIL CONTAINER LABELS (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)
 - i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please remove the statement, (b) (4) which follows the established name. (b) (4) does not appear in the Official USP monograph title for this product.
 - ii. As currently presented, the font utilized for the established name appears to be too thin. Revise the established name to be in accordance with 21 CFR 201.10 (g)(2) so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
 - B. RETAIL CARTON LABELING (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)
 - i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please revise the established name from (b) (4) to (pancrelipase) Tablets. (b) (4) does not comply with the official USP monograph title for Pancrelipase Tablets per the United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27 and 10/1/10-2/1/11, USP 33/NF 28.
 - ii. As currently presented, the “Axcan Pharma” logo on the principle display panel appears large and is more prominent than the strength presentation. Minimize or remove this logo.
 - iii. See comment 3(A)(ii) above.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS will be necessary for Viokace (pancrelipase), if it is approved, to ensure that the benefits of the drug outweigh the possible risks of fibrosing colonopathy and transmission of viral disease to patients. The REMS, should it be approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS, included in your submission dated October 29, 2009, amended on August 20, 2010 and September 17, 2010, 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 22542.”**

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

APPENDIX 3: DS Deficiency Items – First Action

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

1. Provide a list of all contract laboratories that will be used in support of manufacturing your products. Include the specific tests that will be performed by each laboratory, the company name, and address where testing is to be conducted. For each laboratory provide a point of contact including name, phone, fax, and email address.
2. For any contract laboratory used in support of manufacturing your products, provide a copy of the quality agreement between the contract laboratory and the associated manufacturing site.
3. For NDA 022222, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
4. For NDA 022542, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
5. For NDA 022175, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.
6. The establishment inspection report indicates that you have implemented a change in the drug substance intermediate storage container, from (b) (4) white drums to (b) (4) blue drums. Provide the results of studies conducted to demonstrate that the change in storage container will not adversely impact product quality. Specifically, submit the following information:
 - a. Extractable/leachable studies and risk analysis performed on the (b) (4) storage container.
 - b. Evaluation of the quality of pancrelipase manufactured using the (b) (4) containers.
 - c. Available stability data on lots of pancrelipase manufactured using the (b) (4) containers.
 - d. Since your process provides for re-use of the drug substance intermediate storage container, provide the results of validation studies performed to support re-use of the (b) (4) container.

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

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

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

(b) (4)

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



(b) (4)

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



(b) (4)



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

/s/

ANIL K RAJPAL
02/09/2012