CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

Amendment

From: **Emanuela Lacana, PhD**
Division of Therapeutic proteins (DTP)

Through: **Amy Rosenberg, MD**
Division Director, DTP

NDA Number: **22542**
Product: **Viokace**
Sponsor: **Aptalis**

Date of Review: **26 February, 2012**
Due Date of CDTL Memo: **9 February, 2012**

SUMMARY BLAXXXXX USAN --NAME

This amendment documents the introduction of a Post-Marketing Commitment in the approval letter for NDA 22542, which was overlooked in the previous TL memo.
The PMC will states:

(b) (4) commits to revise release specifications after [insert number] lots of 1206 and 1252 drug substance have been manufactured. Final report submitted by [Insert date].

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/s/

EMANUELA LACANA
02/27/2012

AMY S ROSENBERG
02/28/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From:	**Emanuela Lacana, PhD** **Division of Therapeutic proteins (DTP)**
Through:	**Amy Rosenberg, MD** **Division Director, DTP**
NDA Number:	**22542**
Product:	**Viokace**
Sponsor:	**Aptalis**
Date of Review:	**6 February, 2012**
Due Date of CDTL Memo:	**9 February, 2012**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA 22542 for Viokace (pancrelipase) manufactured by Aptalis Pharma US, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Viokace is well controlled, and leads to a product that is safe and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

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 PCV1 (Porcine Circovirus 1). 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, 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]

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]

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

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

11. 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]

EXECUTIVE SUMMARY

This summary covers the responses provided by the firm to the Complete Response letter issued November 28, 2010. Detailed description of drug substance and drug product, product quality control and stability, and conditions of use were covered in the TL memo dated November 10, 2010, uploaded in DARRTS on 23 November, 2010. The memo is attached to this summary in Appendix I, for ease of reference.

The complete response issues related to the drug substance (pancrelipase) and drug substance manufacturer (b) (4) Specifically:

1. *Bacillus cereus* and its enterotoxin were detected in samples of drug substance collected by FDA investigators during the inspection of the manufacturing site. The sponsor and drug substance manufacturer had not adequately addressed this issue during the review cycle.
2. (b) (4) had inadequate bioburden control, in terms of incoming raw materials and cleaning procedures.
3. (b) (4) introduced changes in the manufacturing process of the drug substance that were not submitted in the DMF. Specifically, (b) (4) switched from (b) (4) to (b) (4) intermediate storage containers without performing extractable/leachable studies.
4. (b) (4) received an unfavorable inspectional outcome that resulted in (b) (4) a "withhold recommendation" from the Office of Compliance.

Resolution of the CR issues:

Bioburden controls:

(b) (4) conducted an analysis of the manufacturing process and historical microbiological data. This analysis was reviewed by OPS Micro and an evaluation of the in-process microbial count limits was also performed by the OBP primary reviewer.

(b) (4) implemented a series of step to improve microbial control during the manufacturing process:

1. (b) (4) developed quality agreements with the gland suppliers that ensured (b) (4) This procedure can considerably reduce the microbial load in the incoming raw materials.
2. (b) (4) improved cleaning procedures and implemented equipment cleaning after every batch of drug substance manufactured.
3. (b) (4) revised the in-process limits for microbial counts based on the analysis of historical results. (b) (4) introduced four control points at which limits are proposed: (b) (4) At the (b) (4) and (b) (4) stage, microbial counts are set to be at no more that (b) (4) specifications have been reduced to no more than (b) (4) CFU/g.

The OPS micro group, as well as the OBP primary reviewer, found these actions adequate to ensure appropriate bioburden control and I concur with their assessment.

B. cereus enterotoxin:

Aptalis, the NDA holder, conducted the studies to address the issue of enterotoxin contamination, and provided a letter of authorization to allow (b) (4) to reference the studies.

Briefly, Aptalis demonstrated that the ELISA assay used to detect the enterotoxin was not suitable for this purpose, for the following reasons:

1. The detection system used in the ELISA assay is based on the generation of a colored substrate by [(b) (4)]. Since pancrelipase contains [(b) (4)], the presence of these enzymes can result in a number of false positives. In fact, Aptalis demonstrated that the positive signals obtained with pancrelipase become negative when samples were pre-treated with [(b) (4)], an inhibitor of [(b) (4)].
2. Attempts to develop a Western blot-based assay to detect the enterotoxin demonstrated that [(b) (4)] is rapidly degraded by proteases in pancrelipase API. Western blot detection of [(b) (4)] was achieved only in the presence of protease inhibitors, or when the pancrelipase samples were [(b) (4)] prior to testing. Without these treatments, [(b) (4)] was not detected in pancrelipase API
3. Additionally, [(b) (4)] is now controlling bioburden at low levels. Currently, the highest permitted limits in the [(b) (4)] manufacturing process are [(b) (4)] CFU/g at the [(b) (4)] stage and less than [(b) (4)] CFU/g at the [(b) (4)] stage.

In conclusion, the test approved to detect enterotoxin in food preparations was not suitable for pancrelipase samples. Aptalis also demonstrated that [(b) (4)] in pancrelipase samples (up to 100 ng) is rapidly degraded by proteases in pancrelipase samples. Based on the above points, and the stricter bioburden control implemented by the drug substance manufacturer the OBP reviewer concluded that Aptalis has adequately addressed the issue of *B. cereus* enterotoxin, and I concur with the reviewer's evaluation.

Intermediate containers:

During the inspection of the drug substance manufacturer facility, FDA investigators noted that [(b) (4)] had switched intermediate storage containers from [(b) (4)] to [(b) (4)]. The manufacturer did not conduct extractable/leachable studies and did not inform the Agency of the change. [(b) (4)] conducted an extractable/leachable study on the [(b) (4)] containers, and as a result of this study decided to switch to [(b) (4)] drums. [(b) (4)] provided stability data and product quality studies for the [(b) (4)] container, but failed to address the potential presence of metals leaching into the pancrelipase drug substance. **This issue will be addressed as PMC.**

Issues identified during the review of NDA 22542:

During the review cycle, Aptalis indicated that [(b) (4)] a contract laboratory that performs drug product release and stability testing was transferring the laboratories, personnel and equipments to a different location, [(b) (4)] Aptalis submitted assay transfer reports, deemed inadequate due to the number of samples tested and replicates performed. In addition, no statistical analysis was used to demonstrate equivalency and a robust demonstration of equivalency s critical for potency and dissolution assays. In a teleconference with Aptalis the Agency was informed that [(b) (4)] would only be an alternative drug product testing site and that the primary testing site is Confab. [(b) (4)] removed [(b) (4)] as a contract laboratory to support NDA 22542. This issue was therefore addressed during the review cycle. Additional PMCs relate to revision of release specification and stability protocols (as described in the TL memo in Appendix I) and to PMCs for viral control of pancrelipase as described in Dr Anderson's reviews dated 8/27/2009 and 9/2/2009.

Appendix I: TL memorandum dated November 23, 2010

Team Leader's Memo NDA 22-542

From:	**Emanuela Lacana, PhD** **Division of Therapeutic Proteins (DTP)**
Through:	**Amy Rosenberg, MD** **DTP Division Director**
NDA Number:	**22-542**
Product:	**VIOKACE® (pancrelipase tablets)**
Sponsor:	**Axcan Scandipharm**
Date of Review:	**November 10, 2010**

5 pages of Appendix I have been Withheld in Full immediately following this page as a duplicate copy of the Team Leader's Memo dated November 10, 2010 which can be found in this review

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/s/

EMANUELA LACANA
02/09/2012

AMY S ROSENBERG
02/09/2012

Submission: NDA 22542

Product: VIOKACE

Manufacturer: Aptalis Pharma

Reviewer: Richard Ledwidge, PhD
LC/TL Reviewer: Emanuela Lacana, PhD
Division of Therapeutic Proteins

Recommendation: I recommend approval of NDA 22542. There are two outstanding issues that can be addressed as post-marketing commitments. The issues are outlined below and the final language will be included in the TL memo:

1) To re-evaluate specifications after [insert number] lots are manufactured.

2) To conduct a cumulative stability study with one lot of drug substance near expiry is manufactured into drug product and put on stability.

Deficiency Letter Background:
The data presented below regarding the presence of *Bacillus cereus* and its enterotoxin were initially identified in pancrelipase drug substance produced by [redacted] (b) (4) produces pancrelipase API to support Aptalis Pharma NDA's 22222 and 22542. Aptalis conducted the studies required to address the issue of enterotoxin presence in pancrelipase API and in agreement with [redacted] (b) (4) submitted the studies to support their NDA's.

1) *Bacillus cereus* Diarrheal Enterotoxin

Pancrelipase API is a porcine derived mixture of pancreatic enzymes for patients with exocrine pancreatic insufficiency. During a pre-approval inspection at [redacted] (b) (4) the FDA collected samples from 7 lots of pancrelipase API that tested positive for the presence of *B. cereus* (all 7 lots) and its diarrheal enterotoxin (BDE) (1 lot). As the diarrheal enterotoxin has the potential to cause illness the sponsor was asked to perform a risk assessment and implement a control strategy in order to minimize the safety risk to the patient population.

Reviewer comment: The sponsor's response is acceptable. The sponsor has demonstrated the risk of BDE in pancrelipase API is negligible. The risk assessment and control strategy include the following:

- ***a) The 3M ELISA test to measure BDE in pancrelipase API is not suitable for its intended purpose. Matrix effects with pancrelipase lead to false positives and false negatives as the API contains both [redacted] (b) (4) and proteases respectively.***
- ***b) The concentration of proteases in the API is such that it would degrade a late log/stationary phase Bacillus cereus culture producing BDE in [redacted] (b) (4). Therefore any introduced BDE into the process will be destroyed.***
- ***c) Multiple In-process microbial controls are in place to ensure that BDE will not be produced by B. cereus during the manufacturing process.***

Background:
On a pre-approval inspection the FDA took samples for microbiological analysis from 7 lots of pancrelipase API at [redacted] (b) (4). The testing results are shown below:

Table 1 FDA Report of Analysis 3/11/2010

Sample #	*Bacillus cereus* Diarrheal Enterotoxin	*B. cereus* Results (MPN/g)	*B. cereus* Isolate toxigenic?
565399	Negative	*15 to 93*	Yes
565400	POSITIVE	*23 to 43*	Yes
565401	Negative	*<3 to 23*	Yes
575766	Negative	*7.4 to 43*	Yes
575767	Negative	*23 to 240*	Yes
575768	Negative	*<3 to 43*	Yes
575769	Negative	*23 to 23*	Yes

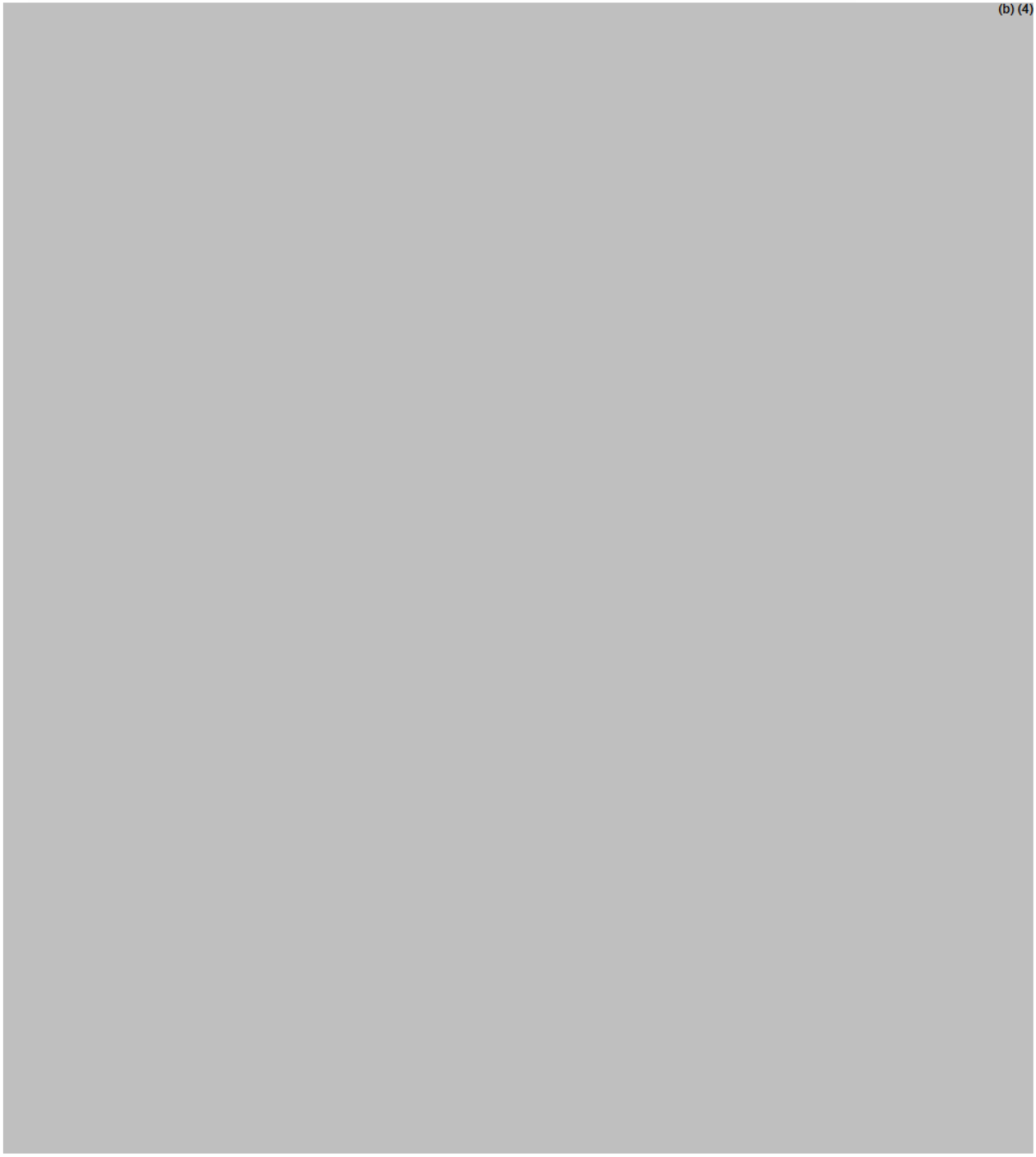
From Form FDA 1551

Bacillus cereus was found in all seven lots, with one lot being positive for diarrheal enterotoxin (BDE). BDE is produced by a complex of three proteins: NheA, NheB and NheC. The disease manifestations caused by bacillus enterotoxin are generally considered mild but the disease spectrum can range from non-toxic to reported death. The disease is caused by vegetative cells/spores that are thought to produce toxin in the small intestine. Ingestion of the BDE complex is not considered dangerous since it is thought to be inactivated by gastric pH and digestive proteases. (b) (4) was asked to perform a risk assessment regarding the inspectional findings and determine the safety risk to patients ingesting pancrelipase API.

A) *Bacillus cereus* diarrheal enterotoxin (BDE) and BDE ELISA Test:

3M sells an ELISA kit to measure BDE. The kit is used in the food industry but has not been validated for testing of pharmaceutical products. The ELISA test is based on detection of the by NheA component of the BDE complex by a specific antibody. (b) (4) tested the ELISA kit to determine if matrix effects (pancrelipase components such as proteases) could impact the accuracy of the assay.

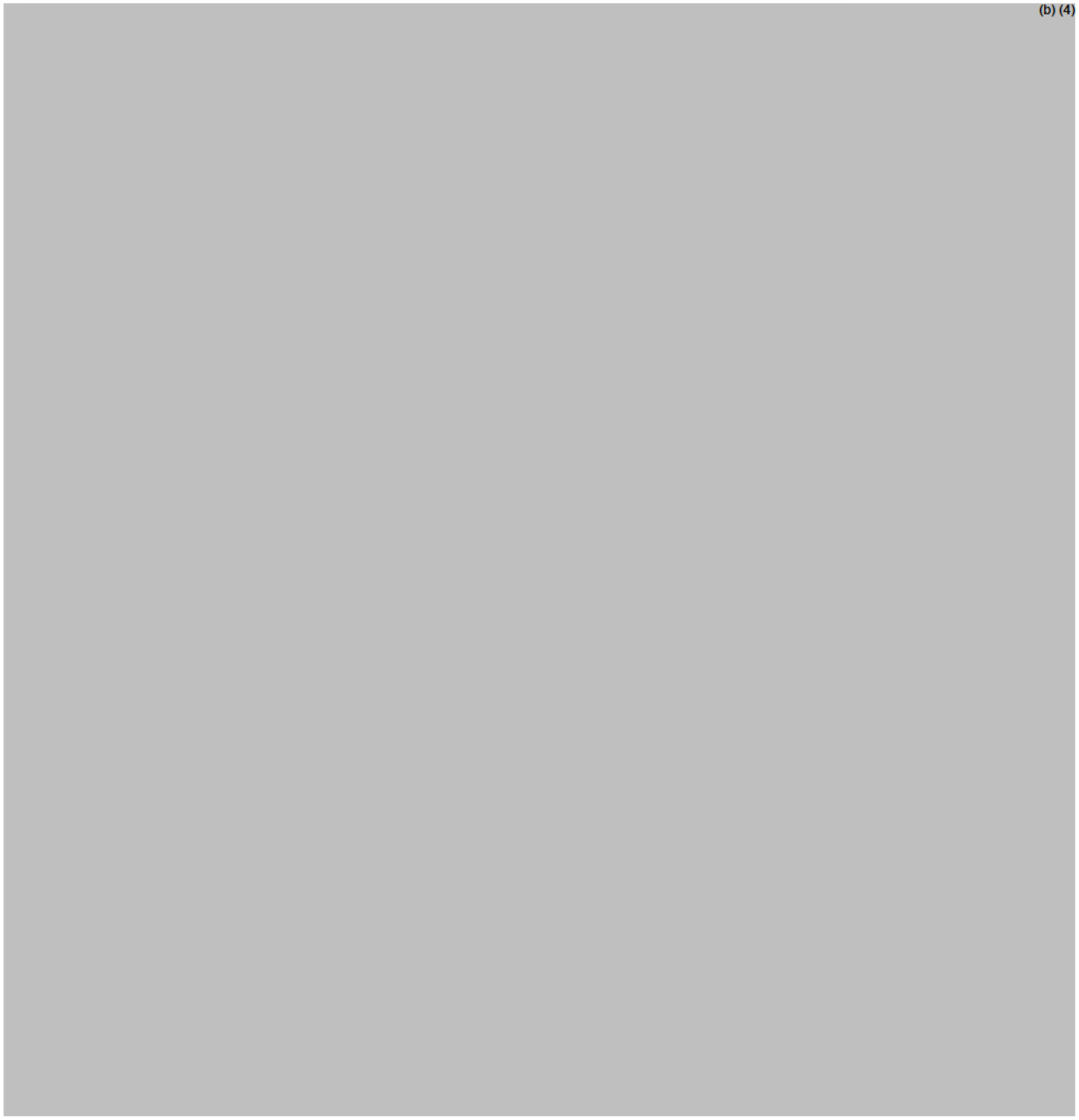
Pancrelipase API contains (b) (4)
Because the ELISA test is based on (b) (4) activity it is possible that (b) (4) in the API could account for the positive results. (b) (4) activity in the API was measured in the presence/absence of (b) (4) (an inhibitor of (b) (4)). As the figures below show, with increasing (b) (4) concentrations, there is a corresponding decrease in the ELISA signal, suggesting that the signal is a consequence of the (b) (4) present in the pancrelipase API.



Pancrelipase API contains proteases

Another concern for the ELISA test is that proteases in the pancrelipase API could degrade BDE and/or the immunoglobulins used to bind BDE. Because of assay interference of proteases, the ELISA kit was unable to accurately detect spiked BDE into API unless API was diluted 10,000-100,000 fold (See figure 3 below). Protease inhibitors were also used to help detect BDE but even at 200X the recommended protease inhibitor concentrations there was significant protease activity and digestion of BDE occurring (See Figure 5 below).

(b) (4)



Reviewer Conclusion on BDE ELISA Test:

The ELISA test is not suitable to detect BDE in the pancrelipase matrix as a result of the presence of (b) (4) ***and proteases in the pancrelipase API. The presence of*** (b) (4) ***leads to false positives, while proteases have the potential to give false negatives by degrading BDE. Another assay that is not subject to interferences in the pancrelipase API is required to detect BDE.***

B) Development of Western Blot Methods to detect BDE and its degradation in pancrelipase API.

The sponsor attempted to overcome interference of the ELISA test by components of the pancrelipase API by using Western blot, and attempted optimization of the Western in several ways, summarized below:

(b) (4)

(b) (4)

(b) (4)

The Western Blot method was used to determine the rate of degradation of spiked BDE into pancrelipase API. Degradation of BDE was both time and pancrelipase API dependent. A summary of the results from the studies conducted is provided below:

(b) (4)

Reviewer Conclusions from Western method to detect BDE in pancrelipase API:
Studies performed by the sponsor demonstrate that any pre-formed BDE will be rapidly degraded during the manufacturing of pancrelipase API. These studies are consistent with what is observed in the scientific literature. The risk of pre-formed BDE being administered to patients is negligible.

C) In process microbial controls to limit BDE production

From the literature, production of BDE typically begins once cell density reaches 10^8cells/ml in rich media but has been shown to occur at a minimal level of 10^5cells/gram. FDA has set a risk threshold of 10^6cells/g in food. The literature also indicates that only middle and late exponential phases of proliferation show BDE production.

The manufacturing process and in-process time points at which samples are taken for microbial counts are shown in the scheme below.

Figure 1: Pancreatin Manufacturing Process

In process limits were set as NMT (b) (4) CFU/g during the (b) (4) process and (b) (4) and NMT than (b) (4) CFU/g for (b) (4) and (b) (4) samples (same as finished API). These limits will ensure that no BDE is produced during manufacturing.
Below are tables summarizing manufacturing history of microbial counts at different points in manufacturing.

Table 2a [redacted] in-process Microbial Test Results for MI 1206 (Pancreatin)

	MI 1206 Data	
	[redacted] TAMC (CFU/g)	[redacted] TAMC (CFU/g)
Average (n=11)	2112	1341
Standard Deviation	2300	1130
Maximum	8900	4600
Minimum	880	580
Specification	NMT [redacted] CFU/g	NMT [redacted] CFU/g

Table 2b: [redacted] in-process Microbial Test Results for MI 1208 (Pancrelipase)

	MI 1208 Data	
	[redacted] TAMC (CFU/g)	[redacted] TAMC (CFU/g)
Average (n=25)	1538	749
Standard Deviation	1057	373
Maximum	4300	1500
Minimum	480	85
Specification	NMT [redacted] CFU/g	NMT [redacted] CFU/g

	MI 1206 Data	
	[redacted] TAMC (CFU/g)	[redacted] CFU/g lot
Average (n=11)	853	249
Standard Deviation	2038	380
Maximum[1]	6900	1000
Minimum	10	10
Specification	NMT [redacted] CFU/g	NMT [redacted] CFU/g

[1]The maximum value represents a single lot, the only lot to fail the NMT [redacted] CFU/g specifications. The lot was investigated, rejected and corrective actions were implemented.

Table 3b: [redacted] in-process Microbial Test Results for MI 1208 (Pancrelipase)

	MI 1208 Data
	[redacted] TAMC (CFU/g)
Average (n=25)	135
Standard Deviation	210
Maximum	1100
Minimum	15
Specification	NMT [redacted] CFU/g

Table 4: [(b) (4)] in-process Microbial Test Results for MI 1208

	[(b) (4)] TAMC (CFU/g)
1208-1794	190, 150, 210, 160, 240, 200, 210, 150, 180, 150, 160, 220,
1208-1795	30, 85, 30, 85, 120, 45, 85, 70, 85, 70
1208-1796	200, 230, 230, 220, 180, 220, 180, 280, 240, 260

Reviewer Conclusions from Microbial Counts in Manufacturing:

There are four points in the manufacturing process whereby samples are taken and microbial counts determined. The acceptance criteria were set so that *B. cereus* is maintained below the cell density at which BDE production takes place (based on scientific literature and sponsor experience). The acceptance criteria were set based on historical results obtained by [(b) (4)] throughout their manufacturing history. Appropriate controls are in place to ensure no BDE production is taking place during manufacturing.

Reviewer Overall Conclusion Bacillus cereus Diarrheal Enterotoxin

The sponsor has demonstrated the risk to patients for BDE contamination in pancrelipase API is negligible. The sponsor has demonstrated that the 3M ELISA test to measure BDE in pancrelipase API is not suitable for its intended purpose due to the presence of enzymes in pancrelipase API that interfere with the detection system and/or affect the integrity of the enterotoxin ([(b) (4)] and proteases respectively). Lastly, multiple in-process microbial controls are in place to ensure that BDE will not be produced by B. cereus during the manufacturing process.

ASSAY TRANSFER

Introduction:

During the review cycle the sponsor communicated to the Agency on November 15, 2011 that they are in the process of transferring all drug product test methods (release and stability) to [(b) (4)] before the end of 2011 due to the expected site closure of [(b) (4)]

Assay Transfer Reports:

The general procedure to establish equivalency of analytical methods at the two sites is shown in the table below:

Table 2 General procedure

Method type	Number of lots	Number of replicates	Acceptance criteria*
Assay	1	2	(b) (4)
Dissolution	1	1	
(b) (4) impurities	1	1	

*All system suitability requirements must be met. The product specifications must be met.

Data from Assay Transfer:
The data in the table below shows the results of the study for lipase enzymatic activity in the pancrelipase API.

Table 4 Assay of Lipase in Pancrelipase capsules

(b) (4)

The acceptance criteria has been met.

Reviewer Conclusion on Assay Transfer:

The limited data to support the transfer of analytical methods for release and stability testing to the (b) (4) testing site is insufficient. The method transfer exercise is inadequate because 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. Furthermore, the use of a single lot of drug product does not evaluate the variability inherent between different test samples. 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 sponsor 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 exercise should include justifications of acceptance criteria and sample sizes.

In a teleconference with Aptalis on 1/30/12 the agency discussed the inadequacy of their submitted method transfer exercise and a regulatory path forward for NDA 22542. Aptalis indicated that for NDA 22542 drug product release testing is primarily performed at Confab Laboratories, Inc in Quebec Canada

and that [redacted] (b) (4) would be used as an alternate site. Aptalis proposed removing [redacted] (b) (4) from list of manufacturers for NDA 22542 until a robust assay transfer exercise is conducted and reviewed by the agency. Aptalis's response is acceptable.

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/s/

RICHARD LEDWIDGE
02/01/2012

EMANUELA LACANA
02/01/2012

Team Leader's Memo NDA 22-542

From:	**Emanuela Lacana, PhD** **Division of Therapeutic Proteins (DTP)**
Through:	**Amy Rosenberg, MD** **DTP Division Director**
NDA Number:	**22-542**
Product:	**VIOKACE® (pancrelipase tablets)**
Sponsor:	**Axcan Scandipharm**
Date of Review:	**November 10, 2010**

SUMMARY OF QUALITY ASSESSMENTS

Recommendation and conclusions on approvability

The Division of Therapeutic Proteins does not recommend approval of NDA22542. Albeit the drug product manufacture is adequate and only few issues remain that can be addressed by Post Marketing Commitments, there are pending issues with the drug substance manufacture that need to be resolved prior to approval of NDA22542:

1. During inspection of (b) (4), inspectors noted that changes to the drug substance intermediate container were introduced into the process, and the DMF holder was cited for lack of extractable leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported. However (b) (4) did not provide validation data or extractable/leachable studies for the new container. This issue was discovered after the primary review was completed and for this reason is not discussed in Wei Guo's review.

2. Both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase from (b) (4) for the presence of *Bacillus cereus* diarrheal enterotoxin and detected the toxin in several samples. (b) (4) claims that the positive results are false positives and are due to matrix interference. However, the DMF holder has provided no data to support this contention.

3. (b) (4)

The following PMCs should be communicated to AXCAN once (b) (4) resolves the issues outlined above. Additionally, PMC 1 and 2 should also be negotiated with (b) (4) once the approvability issues are resolved.

1. *To revise release and stability specifications after 30 lots of drug product have been manufactured.*

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]*

Description of pancrelipase and VIOKACE

Pancrelipase is a complex mixture of proteins obtained from porcine pancreas. Pancrelipase contains amylase, lipase, (b) (4)

Pancrelipase is formulated with excipients (colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, stearic acid, microcrystalline cellulose, and talc) at the drug product manufacturer to manufacture VIOKACE®.

VIOKACE® is the only non-coated pancreatic enzyme product, presented in a tablet dosage form. VIOKACE® is administered orally, concomitantly with proton pump inhibitors, which prevent secretion of acid in the stomach, thereby protecting the enzymes in VIOKACE® from acid inactivation. The tablets are packaged in plastic bottles, containing a desiccant packet to protect from moisture. VIOKACE® is presented in two strengths, based on the lipase activity content: 10440 and 20880 USP units. Historically, the sponsor had manufactured VIOKACE® with a target lipase activity of 8000 or 16000 USP lipase units (hence the qualifiers VIOKACE®8 and VIOKACE®16 found throughout Dr. Guo's review). The sponsor manufactured the product with (b) (4) the sponsor adjusted the label claim to reflect the actual content of lipase in the tablets (10440 and 20880 USP lipase Units) and submitted the NDA.

Mechanism of action

Pancrelipase functions to replace pancreatic enzymes, absent in patients with cystic fibrosis or diseases that cause pancreatic insufficiency. The enzymes contained in pancrelipase are active in the intestinal environment, where they contribute to the digestion of fats, starch and proteins in food. Lipase, amylase and proteases are all potentially active ingredients in pancrelipase. However, clinical efficacy has been demonstrated only for lipase. Lipase requires (b) (4) as a cofactor in a 1:1 ratio for full enzymatic activity. (b) (4) facilitates substrate access and presentation to lipase and in its absence lipase activity is reduced. (b) (4) has demonstrated that (b) (4) is in a 1.5- 2 fold excess of lipase in all pancrelipase batches tested. Therefore, lipase activity is not restricted by limiting amounts of (b) (4) and is consistent from batch to batch of pancrelipase.

VIOKACE® is administered orally, concomitantly with proton pump inhibitors, which prevent secretion of acid in the stomach, thereby protecting the enzymes in VIOKACE® from acid inactivation. The firm conducted a study to evaluate the enzyme activity of VIOKACE® administered with or without omeprazole, following liquid meal stimulation. Samples of intestinal material were evaluated for enzyme activity. The results showed that the samples had statistically significantly greater enzyme activity when VIOKACE® was administered concomitantly with PPI than when administered alone. The Phase III clinical trial demonstrated an improvement in CFA in patients treated with VIOKACE® concomitantly with PPI over the placebo-treated group. The study did not compare VIOKACE® to enteric-coated PEP; therefore there is no information on how efficacious this product is in comparison to enteric-coated products.

Biological activity assay

Three assays are used to assess pancrelipase potency and these assays measure lipase, amylase and protease activities. All assays are performed according to established USP-based methods.

Enzymatic assays measure the conversion of a specific enzyme substrate into a product. The substrate used in the lipase assay is olive oil. The triglycerides contained in the olive oil are hydrolyzed to free fatty acids, and the enzymatic activity is measured by sodium hydroxide titration of the free fatty acids generated. Lipase activity is calculated by comparing the rate of olive oil hydrolysis by the drug substance to the rate of olive oil hydrolysis by a pancrelipase reference standard. Starch is the substrate used in the amylase activity assay. Starch reacts strongly with iodine, turning a deep blue color. Digestion of starch by amylase is measured as reduction in color intensity and the amylase activity is measured by comparing the starch hydrolysis rate by the drug substance or product to the starch hydrolysis rate by a pancrelipase reference standard. Protease potency is measured using casein as a substrate. Casein digestion by protease generates peptides that are soluble after acid treatment of the reaction mixture, in contrast to casein protein, which precipitates out of solution instead. The precipitated casein is filtered off and the amount of soluble peptides is measured by absorbance at 280 nm. Protease activity is calculated by comparing the casein hydrolysis rate by the drug substance or product to the casein hydrolysis rate by a pancrelipase reference standard.

Complexity

The pancreatic extracts have been characterized based upon their enzymatic activities, and by using analytical techniques such as SDS-PAGE and Reverse-Phase HPLC. Western blotting and Mass Spectrometry were employed to identify the RP-HPLC peaks.
The drug substance manufacturing process includes (b) (4) steps that are relevant for viral inactivation: (b) (4) The source material is contaminated by endogenous viruses and infectivity assays are performed on drug substance at release, to demonstrate viral removal. Live and infectious PPV was detected in about 20% of pancrelipase batches. The risk of PPV crossing species and infecting humans is considered minimal (discussed in an advisory committee meeting) and is outweighed by the clinical benefit provided by pancrelipase.

Drug Substance and Product Manufacture:

Drug substance:

Pancrelipase drug substance is manufactured by processing of porcine pancreases. The glands (about (b) (4) /batch of drug substance) are (b) (4) to release the lipase, proteases and amylase. (b) (4) The resulting powder is packaged and shipped to the NDA holder.

Drug substance manufacturing issues that precludes a recommendation for approvability of NDA22542:

During an inspection of the DMF holder facility conducted in May 2010, FDA investigators noted very high microbial counts in in-process materials and collected samples to be analyzed in FDA labs. *Bacillus cereus* was among the microbial specie identified in the samples. Given the presence of the microorganism, FDA tested the samples for the presence of the *Bacillus cereus* diarrheal enterotoxin. Low levels of enterotoxin were detected in samples collected by investigators inspecting the firm, analyzed both in FDA labs in the field and CFSAN. The sponsor should implement an assay that monitors for *Bacillus cereus* enterotoxin. Additional issues that pertain with the ability of the firm to implement an appropriate strategy to control bioburden are discussed in the microbiology review by Steve Langille and will need resolution prior to approval of NDA22-542.

Another manufacturing issue has been highlighted after Dr. Guo completed his review and left the Agency. I reviewed the Establishment Inspection Report prepared by FDA investigators that inspected the firm from (b) (4) As documented in the EIR, the firm changed the drug substance intermediate container from white (b) (4) drums to blue (b) (4) drums. The investigators noted that extractable and leachable studies were not performed. The sponsor did not submit the information to the Agency for review and did not notify the NDA sponsor of the change introduced in the manufacturing process. Since the intermediated is stored in (b) (4), information on the extractable and leachable profile, risk assessment to determine the impact to product quality, stability studies and validation studies are necessary to assess the impact that this manufacturing change could impose on product quality. The information was formally requested but as of November 8, 2010, the Agency has not received a submission from (b) (4). Therefore, we do not recommend approval of NDA 22542.

Drug Product:

The manufacturing process for the drug product is relatively simple and provides for (b) (4) The sponsor validated the manufacturing process and provided the results of the validation study. Holding time validation studies were provided for the (b) (4) holding steps (b) (4) and the results support the proposed hold times. The validation protocol included the following:

- Study to support (b) (4) uniformity. (b) (4) were sampled to measure critical quality attributes. (b) (4) were sampled in duplicate for all tests, except for lipase activity, which was sampled in duplicate in (b) (4). The results provided in the submission are supportive of a process that produces a uniformly (b) (4) product.
- Evaluation of the quality attributes of the product after variation of critical process parameters, such as (b) (4), outside of the pre-determined target limits (process challenging conditions). The quality attributes of the product manufactured under challenging conditions were similar to the quality attributes of the product manufactured at target (b) (4) indicating a robust manufacturing process.

- Evaluation of manufacturing conditions (b) (4) that are not typically monitored as in-process controls during routine operations, to ensure consistency of the production process.

In conclusion, the data provided in the submission support the notion that the manufacturing process has been validated by the sponsor and produces a consistent product that meets its expected quality parameters.

Drug Substance and Product Release Tests:

The release tests for drug substance include the following: appearance, identity by enzyme activity (lipase, protease and amylase) and RP-HPLC, impurities (water, residual solvents, loss on (b) (4) microbial testing), purity/potency by enzyme activity (lipase, protease and amylase). In addition to the drug substance assays described above, drug product testing includes the following: description, (b) (4) uniformity of dosage unit (weight variation), and dissolution. The assays proposed for the release testing program are adequate and allow for control of the critical quality attributes described below. The acceptance criteria for some of the assays are wide, particularly RP-HPLC, because it has been implemented only recently. The same issue applies to stability specifications.

As a PMC, we will request that the sponsor revise the release and stability specifications after 30 lots of drug product is manufactured and release data accumulated.
A similar PMC will be requested of the holder of the pancrelipase DMF.

PMC language:
To revise release and stability specification after 30 lots of drug product have been manufactured.

Critical Product Attributes:

1. Lipase activity: Lipase activity is a critical product attribute linked to both safety and efficacy. Excessive consumption of lipase has been correlated to fibrosing colonopathy in children younger than 12 years of age. The primary efficacy endpoint in clinical studies was the Coefficient of Fat Absorption, which is linked to lipase activity. Lipase activity is the label claim for the product and is controlled at (b) (4) of the label claim.

2. Moisture: Pancrelipase is sensitive to moisture: lipase activity is quickly lost upon exposure to moisture.

3. Dissolution: Dissolution is essential for release of pancreatic enzymes in the environment where they are intended to carry out their therapeutic action.

4. Microbial and viral content: Tests performed on the drug substance and drug product to ensure microbial control include the following: total aerobic microbial count, total combined yeast and mold counts, and specific testing for microbial pathogens Salmonella and Escherichia coli. Extensive viral testing is also included in the drug substance release protocol. *Bacillus cereus* and *Bacillus cereus* toxin were identified in batches of

pancrelipase manufactured at (b) (4). Additional in-process testing to limit the bioburden and a test to assess the presence of the toxin in pancrelipase were included upon request of the microbiology reviewer. However, the positivity of pancrelipase samples for diarrheal enterotoxin is still a concern. Samples analyzed for (b) (4) by (b) (4) were reported as negative. However, during inspection of the contract lab testing, several serious deviations were noted, including the reporting of positive samples as negative. Considering the issues with the testing lab and the fact that (b) (4) has no test in place to monitor for enterotoxin, this issue precludes approval of NDA22-542.

Development and Comparison of Drug Substances:

There have not been significant changes in drug substance or drug product manufacturing.

Degradation and Stability:

Pancrelipase, and particularly the lipase component, is sensitive to moisture. The drug substance DMF holder has shown, with the stressed stability study (40ºC /75% relative humidity) that lipase activity is rapidly declining within the first months from initiation of the study. The NDA sponsor has conducted extensive forced degradation studies to evaluate the effect of various stress conditions on the stability of pancrelipase and found that high temperature, acid and basic pH, oxidation and UV treatment cause degradation of product as assessed by RP-HPLC and enzyme activity assays. The results indicate that both enzyme activity assays and RP-HPLC are stability-indicating. No degradation was found when a photostability study was conducted according to ICHQ1b. The sponsor provided in-use stability studies, conducted under conditions mimicking handling by patients (normal room conditions, opening the bottles 5 times a day). Transportation studies were also conducted (3 times during the study). The results of the study indicate that the product is stable for the 20-day duration of the study. Additionally, the sponsor evaluated temperature excursions of VIOKACE at the beginning and end of the shelf life and demonstrated that the product is stable at both low and high temperature (maximum 40°C) for up to 48 hrs. Drug product should be designated as "protect from moisture" as exposure to moisture reduces lipase activity of the product, and only brief temperature excursion should be allowed. Information to this effect for patients is included in the package insert and Medication Guide.

Although there is a slight downward trend in lipase activity, the results of real-time, real temperature stability studies show that the lipase activity measured meets the stability acceptance criteria at 24 months. Amylase and protease do not show downward trends. The long term stability studies provided support a drug product shelf life of 24 months when stored at 25^{o}C. The sponsor only provided accelerated stability studies. Stress stability studies were not included in the application and the sponsor did not appear to understand our request for stressed stability studies and our reference to ICHQ5C. However, the accelerated stability data submitted by AXCAN show product degradation over time, which is what is needed to determine that the assay are stability-indicating and to establish a degradation profile. Therefore, although the stability studies were not conducted according to ICHQ5C, because a stressed condition was not included, they are sufficient to establish the stability profile of the product. There are two additional issues to take into consideration:

- The NDA did not include information on stability of drug product manufactured with drug substance at the end of shelf life.
- The proposed annual stability protocol commitment is adequate. However, we recommend that the sponsor also include accelerated and/or stressed conditions. These conditions are better suited than the storage conditions to reveal changes in product quality attributes that may result from minor changes to the product (changes in personnel, minor equipment changes) that occur over time. This issue is in common with the drug substance manufacturer.

These issues can be addressed as PMC.

In regard to drug substance, a shelf life of 24 months at 25ºC is currently recommended based upon information submitted by the sponsor.

PMC language:
To include accelerated and/or stressed stability conditions in the annual stability protocol. The updated protocol will be provided by: date

To evaluate stability of drug product manufactured using drug substance at the end of the shelf-life. Stability data will be provided by: date

Description of How the Drug Product is Intended to be Used

VIOKACE® is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. VIOKACE® is orally administered, concomitantly with Proton Pump Inhibitors. In contrast to other PEPs, VIOKACE is not enteric-coated. Concomitant medication with PPI is necessary to reduce the acidity of the stomach content and protect the enzymes form degradation prior to reaching the intestinal lumen. As for other PEPs, therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of VIOKACE® should be individualized based on clinical symptoms, degree of steatorrhea and the fat content of the diet. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.
VIOKACE® is supplied in a tablet dosage form, at either 10440 or 20880 USP Lipase Units. The bottles contain a desiccant packet to protect from moisture.
VIOKACE® should be stored at 25ºC and protected from moisture. The recommended expiration dating period for VIOKACE® is 24 months under these storage conditions. Based on the results of the stressed studies submitted, patients should be instructed to keep bottles tightly closed between uses. This recommendation is provided in the package insert and Medication Guide.

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/s/

EMANUELA LACANA
11/23/2010

AMY S ROSENBERG
11/23/2010

Submission: **NDA 22542**
Product: VIOKACE® (Pancrelipase, USP) Tablets
VIOKACE® 8, VIOKACE® 16 Tablets
Indication: Exocrine pancreatic insufficiency
Formulation: Oral, tablet, non-coated

Sponsor: Axcan Pharma US, Inc.

CMC Reviewer: Wei Guo, Ph.D., HFD-122
Through: Emanuela Lacana, Ph.D., HFD-122, Associate Chief, Lab of Chemistry

Review Date: May 5, 2010
Revised Date: August 26, 2010
September 23, 2010

Conclusions: I do not recommend approval of this submission. At this time (9/23/10) the compliance status of the (b) (4) facility is still under evaluation and there are issues with the presence of diarrheal Bacillus cereus enterotoxin in the drug substance. The approvability of this NDA is pending on the successful resolution of these issues.

The following additional issues can be addressed as Post-Marketing Commitments:

1. **Add stability testing under stress condition (40°C/75% RH) in the annual stability program.**
2. **Revise release and stability specifications after 30 lots of drug product are manufactured.**

INTRODUCTION

This proposed product received Fast Track designation on May 10, 2007 under IND 60716. Rolling submission was permitted by FDA as indicated in a letter dated April 10, 2009. The Non-Clinical Pharmacology and Toxicology unit was submitted on April 28, 2009. The CMC unit was submitted on July 2009 and the NDA submission was completed on October 30, 2009, when the clinical section was submitted.

A request for categorical exclusion from environmental assessment is provided in the submission. Categorical exclusion is acceptable for this application, which involves a biological product that occurs naturally in the environment, as described in the FDA Guidance "Environmental Assessment of Human Drug and Biologics Applications". Approval of this NDA will not alter significantly the concentration or distribution of the substance or its degradation products in the environment therefore based on regulations established in part 21 CFR 25.31 (c), I recommend approval of this request.

This review is focused on CMC only. This submission is CTD formatted, and is reviewed in that order. Reviewer's evaluation is written in italic, comments to sponsor are written in bold.

3.2.S DRUG SUBSTANCE

The sponsor referenced Type II DMF (b) (4) for drug substance, which is manufactured by (b) (4). It is stated in the submission that drug substance, Pancreatic Enzyme Concentrate (PEC) 1252, is used in the manufacturing of the VIOKACE tablets.

Authorization letter from DMF (b) (4) dated July 20, 2009 is provided.

According to DMF (b) (4) drug substance 1252 is (b) (4) drug substance 1206. DMF (b) (4) is reviewed separately to ensure the CMC information regarding the drug substance is current and adequate.

The GMP status of (b) (4) was determined as inadequate as of (b) (4). The (b) (4) facility will be re-inspected to verify that the corrective actions are adequate. Approval of this NDA will require a favorable resolution of inspectional issues. (b) (4) was re-inspected in (b) (4) and the inspection closed the first week of (b) (4). At this time, we do not have a recommendation from office of Compliance and approval of this application will be pending resolution of issues identified during the inspection. An additional issue that should be resolved relates to the presence of Bacillus cereus enterotoxin and the non-compliant status of the testing facility used by the DMF holder. Approval of the NDA will also be dependent on satisfactory resolution of this issue.

3.2.P DRUG PRODUCT

3.2.P.1 DESCRIPTION AND COMPOSITION

The currently market product is named VIOKASE. The new name is VIOKACE. No changes to the formulation or the ingredients were introduced and the Currently Marketed Product (CMP) has the same API and formulation as the To be Marketed Products (TbMP).

VIOKACE® (Pancrelipase, USP) is manufactured as a tablet dosage form, containing lipase, amylase and protease activities. The API for this drug product is the extract of porcine pancreatic enzyme concentrate (pancrelipase).

VIOKACE® 8 is a round shaped, biconvex tablet engraved with "9111". VIOKACE® 16 is an oval shaped, biconvex tablet engraved with "9116". The dosage strengths (enzyme activities) for VIOKACE 8 and VIOKACE 16 are:

Enzymes	VIOKACE® 8	VIOKACE® 16
Lipase	10,440 USP units	20,880 USP units
Amylase	39,150 USP units	78,300 USP units
Protease	39,150 USP units	78,300 USP units

The drug product composition is listed in the following table:

Component	Function of Component	VIOKASE® 8 10,440 USP Units Lipase [1] 39,150 USP Units Amylase 39,150 USP Units Protease		VIOKASE® 16 20,880 USP Units Lipase [1] 78,300 USP Units Amylase 78,300 USP Units Protease	
		Amount per Unit	%	Amount per Unit	%
Pancreatic Enzyme Concentrate (b) (4) USP	Active Ingredient				(b) (4)
Microcrystalline Cellulose, NF	(b) (4)				
Croscarmellose Sodium, NF					
Lactose Monohydrate, NF					
Stearic Acid, NF					
Colloidal Silicon Dioxide, NF					
Talc, USP					
Total	-				(b) (4)

The following comment was sent to the sponsor in June 2010:

"Clarify whether the to-be-marketed product (TbMP) is the same formulation as the previously marketed product (PMP).

a) If the TbMP and PMP are the same formulation: identify how long the PMP was marketed, and identify the approximate date at which postmarketing data for the PMP first became available.
b) If the TbMP and PMP are not the same formulation: provide a brief description of the changes in the formulation."

The sponsor stated in a submission dated June 29, 2010 that TbM and PMP have the same formulation and are identical.

The response is acceptable.

This product is marketed in white HDPE (high density polyethylene) plastic bottles. Each bottle contains 100 tablets with desiccant pouch (b) (4) secured with a (b) (4) cap lined with a heat induction foil inner seal.

The drug product VIOKACE 8 and VIOKACE 16 have (b) (4) The labeled lipase activity does not include (b) (4)

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

VIOKACE® is a non-enteric coated tablet. In order to prevent the API, consisting of acid-labile enzymes, from being destroyed in the acidic condition that arise in the stomach, the sponsor stated that this product will be prescribed with proton pump inhibitors (PPI), which block the production of acid in the stomach.

The firm cited an intestinal study recently completed by Axcan Pharma Inc. The firm contends that VIOKACE®16 administered with omeprazole following liquid meal stimulation had statistically significantly greater clinical efficacy than VIOKACE®16 administered alone.

The Medical officer and the Clinical pharm reviewer will determine if this product has acceptable efficacy.

3.2.P.3 MANUFACTURE

3.2.P.3.1 Manufacturer(s):

The facilities involved in manufacturing VIOKACE are listed below:

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/s/

WEI GUO
09/23/2010

EMANUELA LACANA
09/24/2010

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
NDA 22542	Axcan Pharma US, Inc.	July 30, 2009
Established/Proper Name:	BLA/NDA Type:	
(VIOKASE)	NDA	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	Draft label is provided in SPL format, the proprietary name is yet to be decided.

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing arrangement	N/A	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	Drug substance information is provided in DMF (b) (4)
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	Y	
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	N/A	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y	
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
o justification of specifications		
o stability		

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance		
❑ control of drug substance		
o specifications		
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation		
o batch analyses		
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		Process validation is performed in 2003, need update.
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	Y	
o container-closure integrity	Y Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	N	
o Filter validation		
o Component, container, closure depyrogenation		

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent ❑ pharmaceutical development o preservative effectiveness o container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through	N/A	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer sterilization validation o Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part	N/A	

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients		
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N/A	
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	N/A	
Data demonstrating comparability of	N/A	

Examples of Filing Issues	Yes?	If not, justification, action & status
product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	N/A	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product		Facility information of drug substance (b) (4) is provided in DMF (b) (4), no facility information provided for the drug product manufacturer.
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wei Guo	12/23/2009
Product Quality Reviewer(s)	Date
Branch Chief/Team Leader/Supervisor	Date
Division Director	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

WEI GUO
12/23/2009

EMANUELA LACANA
12/23/2009

GIBBES R JOHNSON
12/24/2009