

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-222Orig1s000**

**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:** 22222  
**Product:** Ultresa  
**Sponsor:** Aptalis

**Date of Review:** 6 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 22222, which was overlooked in the previous TL memo.

The PMC will states:

(b) (4) commits to revise release specifications after [insert number] lots of 1208 and 1286 drug substance have been manufactured. Final report submitted by [Insert date].

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/s/  
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EMANUELA LACANA  
02/28/2012

AMY S ROSENBERG  
02/28/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration  
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## The Quality Team Leader's Executive Summary

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

**Through:** Amy Rosenberg, MD  
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**Date of Review:** 6 February, 2012  
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**I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY**

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA 22222 for Ultresa (pancrelipase) manufactured by Aptalis Pharma US, Inc.. The data submitted in this application are adequate to support the conclusion that the manufacture of Ultresa 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 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]

SUMMARY BLAXXXXX USAN --NAME

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 descriptions 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) (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.

All other sections of NDA 22222 and DMF 15681 (supporting drug product manufacture of Ultresa) were reviewed and were deemed adequate. A few remaining issues will be addressed as Post-Marketing Commitment, as outlined in the Approval/PMC section.

**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 steps to improve microbial control during the manufacturing process:

1. (b) (4) developed quality agreements with the gland suppliers that ensured (b) (4) (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) (b) (4). At the (b) (4) and (b) (4) stage, microbial counts are set to be at no more than (b) (4) (b) (4) (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) 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 22222:

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 equipment to a different location, (b) (4) (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 is critical for potency and dissolution assays. To resolve this issue, Aptalis proposed one of their own alternative testing sites located at Pessano, Italy. The Italian site is approved to perform drug product testing related to NDA 22222, except for HPLC and Karl Fisher testing. This issue was discussed internally and it was concluded that the new facility, (b) (4) could perform RP-HPLC and Karl Fisher testing to support NDA 22222, based on the following:

1. The RP-HPLC assay is a qualitative method used to ensure process consistency based on the evaluation of the chromatographic profile compared to a reference standard.

2. Although the data to support equivalency was not ideal, the risk to product quality was assessed to be minimal, because the variability observed between peaks was much smaller than the acceptance criteria established for peaks or groups of peaks.
3. The Karl Fisher assay is a compendial assay, the variability between sites was very low and thus the risk to product quality is negligible.

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 Memo NDA 22222**

**From:** Emanuela Lacana, Ph. D  
Division of Therapeutic proteins (DTP)

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

**NDA Number:** 022222  
**Product:** Pancrelipase (ULTRESA)  
**Sponsor:** Axcen Pharmaceutical, Inc.

**Date of Review:** November 10, 2010

## SUMMARY OF QUALITY ASSESSMENT

**Recommendation and conclusions on approvability**

The Division of Therapeutic Proteins does not recommend approval of NDA22222. Albeit the drug product manufacture is adequate and only few issues remains 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 NDA22222:

1. During inspection of (b) (4) inspectors noted that changes to the drug substance intermediate container were introduced in the process, and the DMF holder was cited for lack of extractable/ leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported, however (b) (4) did not provide validation data or extractable/leachable studies for the new container. 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 results are false positive and that the false positive results are due to matrix interference. However, the DMF holder has provided no data to support this contention.
3. (b) (4)

The following PMCs should be communicated to AXCAN once (b) (4) resolves the issues outlined above. These PMCs should be negotiated with EURAND as well as (b) (4) once the approvability issues are resolved.

12. *To revise release and stability specification after 30 lots of drug product have been manufactured.*
13. *To include accelerated and/or stressed stability conditions in the annual stability protocol. The updated protocol will be provided by: [Insert date]*

The following PMC should be negotiated with EURAND, the drug product manufacturer:

*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 ULTRESA**

ULTRESA is a solid dosage form of pancrelipase, a porcine pancreatic extract containing lipases, amylases and several proteases, used to replace the enzymes which cannot be produced

by a non-functional human pancreas. The pancreatic extracts are manufactured by (b) (4) and are provided to the drug product manufacturer in the form of an amorphous powder. Information on drug substance manufacture is submitted in (b) (4). The drug product manufacturer, EURAND, (b) (4) Information on drug product manufacture is submitted in DMF 15681. The bulk capsules are shipped to Axcan, the NDA holder, which packages, labels and markets ULTRESA. The capsules are filled in (b) (4) bottles with a (b) (4) cap and a desiccant packet is inserted in each bottle, to protect the product from moisture.

### **Mechanism of Action**

Pancrelipase functions to replace pancreatic enzymes, absent in patients with cystic fibrosis or other disease mediated pancreatic insufficiencies. 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.

### **Potency Assays to Measure Activity.**

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) (b) (4) (b) (4) and (b) (4) (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 (the subject of an advisory committee meeting) and is outweighed by the clinical benefit provided by pancrelipase.

### Manufacturing Process

Drug Substance and Product Manufacture: Pancrelipase drug substance is manufactured by processing of porcine pancreases. The glands (about (b) (4)/batch of drug substance) are (b) (4) ( ( (w) (w) to release the lipase, proteases and amylase. (b) (4)

The manufacturing process for the drug product consists (b) (4)

The process has been validated and produces a consistent product that meets its expected quality parameters.

### Drug substance manufacturing issues that preclude a recommendation for approvability of NDA22222:

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 species 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 in CFSAN. The sponsor should implement an assay that monitors for *Bacillus cereus* enterotoxin. Additional issues that pertain to 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) to (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 on the new drums. 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 intermediate is stored in (b) (4) for (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 22222.

**Drug substance and drug product release testing:**

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: (b) (4) content of microtablets, mean weight of pellet/capsule, dissolution of pancrelipase pellets, and free phthalic acid. The NDA sponsor and (b) (4) were asked to tighten acceptance criteria for the RP-HPLC assays and both firms tightened the release and stability specification for RP-HPLC. Although the release and stability specification are adequate, the sponsor and DMF holders should revise the acceptance criteria for amylase and protease, after 30 lots of drug substance and drug product have been manufactured as a Post-Marketing Commitment,. The same commitment should be proposed for (b) (4) AXCAN and EURAND.

**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.
2. Moisture: Pancrelipase is sensitive to moisture: lipase activity is quickly lost upon exposure to moisture.
3. Dissolution: Dissolution of microspheres is essential for release of pancreatic enzymes in the intestine, 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: total aerobic microbial count, total combined yeast and mold counts, and assays to specifically assess for Salmonella and Escherichia coli. Extensive viral testing is also included in the drug substance release protocol. *Bacillus*

*cerus* 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 measure for 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 positive samples reported 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 would preclude approval of NDA22-222.

### **Development and Comparison of Drug Substances:**

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

### **Stability**

The recommended shelf-life for drug substance and drug product is (b) (4) months. Real-time stability data were provided to support the proposed expiry. The drug substance manufacturer (b) (4)

(b) (4), the firm did not conduct worst case scenario studies, where drug product is manufactured with drug substance near the end of the shelf-life. However, we recognize that the DMF holder does not have all the information available on drug substance stability, since the drug substance is manufactured under DMF (b) (4) by (b) (4). In fact, the DMF 15681 holder may only have the expiration date of the drug substance, therefore standard cumulative studies are hard to conduct. This is the reason why we will request the DMF holder to address this issue as PMC.

### **Proposed PMC language (for EURAND):**

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

Axcan provided in-use stability studies, where the bottles were opened five times a day for a month and the activity of the enzymes measured. The product was stable under these conditions. Photostability studies indicated that the product is not sensitive to light. Pancrelipase, and particularly the lipase component, is sensitive to moisture. Lipase activity is quickly lost by exposure to moisture and temperatures of 40°C. The recommendation in the package insert is to store the capsules in a dry place at temperatures not higher than 25°C.

The sponsor has proposed an adequate annual stability protocol. 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 can be addressed as PMC and should be conveyed to (b) (4) EURAND and AXCAN:

### **Proposed PMC language:**

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

**Description of How the Drug Product is Intended to be Used**

- ULTRESA is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. ULTRESA is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of ULTRESA should be individualized based on clinical symptoms and the fat content of the diet. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.
- ULTRESA is supplied in gelatin capsules with the following lipase strength/capsule: 13800, 20700 and 23,000. ULTRESA capsules are supplied in bottles with 100 and 500 counts (for the 23,000 lipase Unit only). The bottles contain a desiccant packet to protect from moisture.
- ULTRESA should be stored at room temperature ( (b) (4) ) and protected from moisture. The recommended expiration dating period for ULTRESA capsules is 24 months under these storage conditions. Based on the results of the stressed studies submitted to evaluate in-use stability, patients should be instructed to keep bottles tightly closed between uses and keep the product in the original container. Information to this effect is outlined in the package insert.

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/s/  
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EMANUELA LACANA  
02/09/2012

AMY S ROSENBERG  
02/09/2012

**Submission: NDA 22222**

**Product: Ultrase<sup>®</sup> MT**

**Manufacturer: Aptalis Pharma**

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

**Recommendation: I recommend approval of NDA 22222. 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 (b) (4) Inc (b) (4) produces pancrelipase API to support Aptalis Pharma NDA's 22222 (b) (4) Aptalis conducted the studies required to address the issue of enterotoxin presence in pancrelipase API and in agreement with (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 (b) (4) (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 (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 (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 (b) (4) The testing results are shown below:

Table 1 FDA Report of Analysis 3/11/2010

Sample #	<i>Bacillus cereus</i> Diarrheal Enterotoxin	<i>B. cereus</i> Results (MPN/g)	<i>B. cereus</i> 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

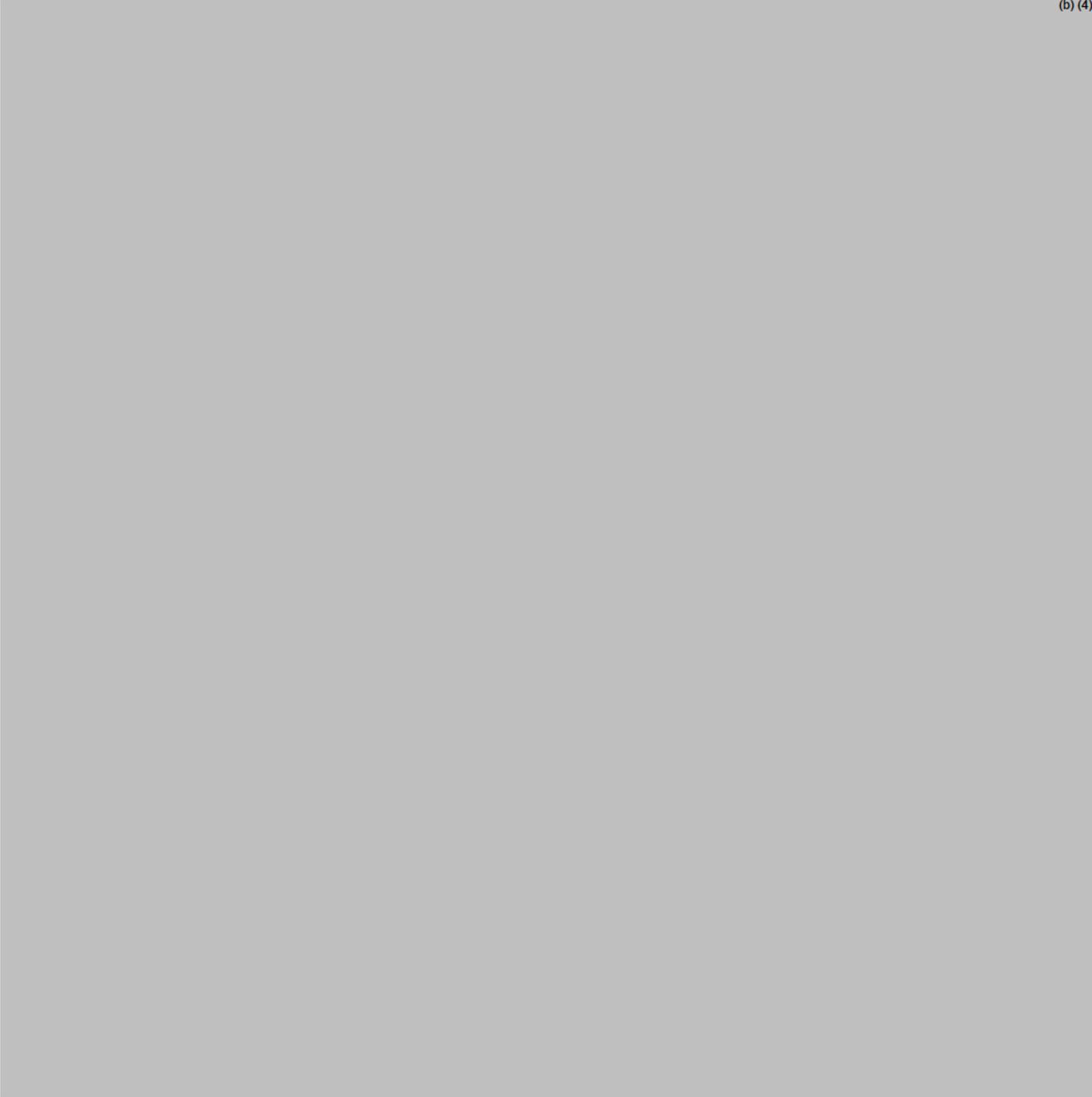
*Bacillus cereus* was found in all seven lots, with one lot being positive for diarrheal enterotoxin (BDE). BDE is produced by a complex of three proteins: NheA, NheB and NheC. The disease manifestations caused by bacillus enterotoxin are generally considered mild but the disease spectrum can range from 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)

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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)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers approximately three lines of text.**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  $10^8$  cells/ml in rich media but has been shown to occur at a minimal level of  $10^5$  cells/gram. FDA has set a risk threshold of  $10^6$  cells/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) (b) (4) and NMT than (b) (4) CFU/g for (b) (4) and (b) (4) - (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: (b) (4) in-process Microbial Test Results for MI 1206 (Pancreatin)

	MI 1206 Data	
	(b) (4)	(b) (4)
	TAMC (CFU/g)	TAMC (CFU/g)
Average (n=11)	2112	1341
Standard Deviation	2300	1130
Maximum	8900	4600
Minimum	880	580
Specification	NMT (b) (4) U/g	NMT (b) (4) CFU/g

Table 2b: (b) (4) in-process Microbial Test Results for MI 1208 (Pancrelipase)

	MI 1208 Data	
	(b) (4)	(b) (4)
	TAMC (CFU/g)	TAMC (CFU/g)
Average (n=25)	1538	749
Standard Deviation	1057	373
Maximum	4300	1500
Minimum	480	85
Specification	NMT (b) (4) CFU/g	NMT (b) (4) CFU/g

MI 1206 Data		
	(b) (4)	(b) (4)
	TAMC (CFU/g)	CFU/g lot
Average (n=11)	853	249
Standard Deviation	2038	380
Maximum <sup>1</sup>	6900	1000
Minimum	10	10
Specification	NMT (b) (4) CFU/g	NMT (b) (4) CFU/g

<sup>1</sup>The maximum value represents a single lot, the only lot to fail the NMT (b) (4) CFU/g specifications. The lot was investigated, rejected and corrective actions were implemented.

Table 3b: (b) (4) in-process Microbial Test Results for MI 1208 (Pancrelipase)

MI 1208 Data	
	(b) (4)
	TAMC (CFU/g)
Average (n=25)	135
Standard Deviation	210
Maximum	1100
Minimum	15
Specification	NMT (b) (4) 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) (b) (4) before the end of 2011 due to the expected site closure of (b) (4) (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 22222. Aptalis proposed that instead of conducting a robust assay transfer exercise for (b) (4) they will use Aptalis Pharma SRL in Pessano con Bornago, Italy to perform drug product release testing. Aptalis Pharma SRL is approved for all drug product release testing related to NDA 22222 except for HPLC and Karl Fisher testing. Aptalis reached an agreement with (b) (4) to continue to perform the HPLC and Karl Fisher testing at (b) (4). Performing the HPLC and Karl Fisher tests at (b) (4) is acceptable. However, we provided Aptalis with the option to perform the HPLC and Karl Fisher tests at (b) (4) as Aptalis originally planned. We made this decision because, although we typically expect a more robust assay transfer exercise for a HPLC impurity test and although the HPLC data showed slight bias upon moving it to (b) (4) we concluded that the amount of variation observed between the two sites is acceptable. A robust equivalency test is not required for this HPLC assay in part because the acceptance criteria for peak sizes are wide and thus we concluded that there would not be much to be gained by performing equivalency testing. In addition the HPLC assay is not measuring known attributes that have been linked to safety and efficacy and thus the risk is considered negligible. The data to support Karl Fisher testing at (b) (4) is also acceptable. From DTP's perspective, Aptalis can perform HPLC and Karl Fisher drug product testing at either (b) (4) or (b) (4).

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RICHARD LEDWIDGE  
02/01/2012

EMANUELA LACANA  
02/01/2012

**Submission:** NDA 22222  
**Product:** Ultrase<sup>®</sup> MT 12, 18, and 20 Capsules  
**Indication:** Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions  
**Formulation:** Oral, capsule, enteric coated minitablets

**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: July 19, 2010

Recommendation:

**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.**

- 1. The following issues can be addressed as PMC:  
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.**

**CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

This submission dated May 27, 2009 is the response to FDA's letter dated May 5, 2009.

The sponsor's responses are evaluated below; the reviewer's evaluation is in italic.

Product Quality:

1. The (b) (4) (b) (4) (b) (4) DMF # (b) (4) and the EURAND DMF #15681 have been reviewed in support of NDA 022222 and found to contain deficiencies. Letters have been sent to (b) (4) and EURAND listing the deficiencies. (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when (b) (4) and EURAND have submitted the requested information.

Response: The sponsor responded that (b) (4) (DMF (b) (4) and Eurand (DMF 15681) have informed the sponsor that updates have been sent to the Agency.

*Evaluation: The DMFs response to the deficiencies have been reviewed and found adequate to support this NDA.*

2. We noted a discrepancy in the description of the capsules printing between your NDA submission and the description provided in the package insert. Please amend your NDA submission to be consistent with the information provided in the package insert.

Response: The sponsor has updated the capsule printing, they are consistent with the information provided in Package Insert now.

Capsules strength	Description
13,800 USP Units of Lipase	(b) (4)
20,700 USP Units of Lipase	
23,000 USP Units of Lipase	

*Evaluation: Acceptable.*

Additional items discussed at a May 20, 2010 Type A meeting between the Agency and Axcan:

1. The Agency requested that the finished drug product specifications for the RP-HPLC test be tightened to (b) (4) standard deviations, with the agreed upon changes to the lower specification for peaks 1, 2 and 6.

Response: The sponsor has updated the specifications of RP-HPLC.



*Evaluation:* The new specification reflects the revised (b) (4) SD) acceptance criteria, with lower limit of (b) (4) for peak 1&2, and (b) (4) for peak 6. It is acceptable.

2. The Agency requested that Axcan provide clarification in the NDA that release and stability tests conducted on the active pharmaceutical ingredient used for the finished drug product in clinical studies were conducted by (b) (4)

Response: The sponsor confirmed that release and stability data generated for the API used for clinical study drug in Axcan studies UMT20CF05-01 and UMT20CF07-01 were generated at (b) (4)

*Evaluation:* The NDA and (b) (4) are updated to reflect this information. This is acceptable.

3. The Agency requested that Axcan provide clarification in the NDA that release and stability tests conducted on the active pharmaceutical ingredient used for commercial finished drug product are conducted by (b) (4)

Response: The sponsor confirmed that release and stability data generated for the API used to support commercial product shelf-life were generated at (b) (4)

*Evaluation:* The NDA and (b) (4) are updated to reflect this information. This is acceptable.

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/s/

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WEI GUO  
09/23/2010

EMANUELA LACANA  
09/24/2010

**Submission:** NDA 22222  
**Product:** Ultrase<sup>®</sup> MT 12, 18, and 20 Capsules  
**Indication:** Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions  
**Formulation:** Oral, capsule, enteric coated minitablets

Review Date: April 29, 2010

Recommendation:

**The sponsor of this application will receive a complete response letter due to deficiencies identified in the Drug Master File that supports the manufacture of the Drug Substance, DMF (b) (4) by (b) (4). The major deficiency identified by the microbiology reviewer was that the failure by the drug substance manufacturer to adequately ensure the microbial quality of the drug substance.**

**We have the following comment to the sponsor:**

**We noted a discrepancy in the description of the capsules printing between your NDA submission and the description provided in the package insert. Please amend your NDA submission to be consistent with the information provided in the package insert.**

## CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

This submission dated October 30, 2009 is the response to FDA's letter dated September 9, 2009.

The sponsor's responses are evaluated below, the reviewer's evaluation is in italic:

### FDA Comment-1:

**The (b) (4) DMF # (b) (4) and the EURAND DMF #15681 have been reviewed in support of NDA 22,222 and found to contain deficiencies. Letters will be sent to (b) (4) and EURAND listing the deficiencies. (b) (4) and EURAND should address the deficiencies by directly submitting information to their respective DMFs. Please notify us when (b) (4) and Eurand have submitted the requested information.**

Response:

The sponsor stated that the holders of DMF # (b) (4) ( (b) (4) and DMF #15681 (Eurand) have updated their DMFs in responses to their deficiencies letters.

*The responses of DMF holders are reviewed separately in the DMF reviews.*

### FDA Comment-2:

**Your annual stability data (Batches D070151C, D070151A, F070244B, F070244A, F070224D, F070224A, D070145B, C080114D, C080114C, D080118A, D080118C, D080151C, C080115A, D080119A) indicate that stability tests are performed before the product is packaged in its final container/closure system. Clarify if all stability studies you have performed were conducted on drug product prior to final packaging. Stability studies should be performed on packaged drug product using the final container/closure system.**

Response:

The sponsor stated that all stability studies have been performed on packaged drug product using the final container/closure system. The sponsor incorrectly reported the dates the product was entered in the stability protocol in the "On stability (dd/mm/yyyy)" field in the Stability Data Summary Tables. The stability summary tables have been amended with the correct dates. The amended stability tables are provided in Section 3.2.P.8.3, Appendix 5.

*The amended stability tables provided in the response were examined, and the corrections have been made on the dates of "on stability". The response is acceptable.*

### FDA Comment-3:

**Submit stability data collected using the updated stability program and acceptance criteria submitted in the NDA.**

Response:

The sponsor provided updated stability summary data and acceptance criteria for 3 MT12 lots. These lots were tested according to the updated stability program.

The updated stability specifications include:

Test	Method	Specification
(b) (4)		

*The acceptance range for the RP-HPLC the peak/peak groups identified is not acceptable. The acceptance range has been established as the mean peak area value  $\pm$  (b) times of SD, using values obtained from 37 lots of drug substance. This approach is (4) not appropriate because it allows 99.7% of the samples tested to be considered acceptable for large variability in the product and does not ensure adequate control of product quality.*

*The sponsor provided updated specifications for RP-HPLC and (b) (4) content test. The sponsor committed to put three lots of MT12 and MT20 to support the 24 months proposed shelf life for the 100 and 500 count packaging formats, (b) (4)*

*In addition, the sponsor updated the on-going stability data with updated specifications for RP-HPLC and (b) (4) content for three MT12. The data are all within the set specifications, but testing occurred at one test station only. Therefore no trending data are available. More data on RP-HPLC profiles and (b) (4) content are necessary. Since the lipase activity is the most sensitive indicator of product stability, these data can be submitted as Post-Marketing Commitment. However, the sponsor of this application will receive a complete response letter due to deficiencies in DMF (b) (4) that supports drug substance manufacturing; therefore a comment will be sent to the sponsor in the CR letter.*

The acceptance limit for Loss on Drying (NMT <sup>(b)</sup>0.0%) <sup>(b)</sup>(4) <sup>(b)</sup>(4). The current LOD acceptance limit for the bulk capsulated drug product release test performed by the drug product manufacturer (Eurand, DMF 15681) has been updated to NMT <sup>(b)</sup>%. Therefore, I recommend that the acceptance limit for LOD proposed by the sponsor of this NDA <sup>(b)</sup>(4) <sup>(b)</sup>(4).

On March 24, 2010, a telecon was held between FDA and Axcan. The following issues were clarified as:

- 1) Who is responsible for finished drug product release testing.
- 2) Justify the acceptance criteria of RP-HPLC in drug product release specification.
- 3) Justify the different LOD acceptance limit of finished drug product and the bulk drug product.

The Sponsor responded in the meeting and in a subsequent submission dated March 26, 2010:

- 1) Axcan is responsible to perform the finished drug product release testing, according to the drug product release specification.

*This response is acceptable; the release test performed by drug product manufacturer (Eurand) is in addition to the finished drug product test.*

- 2) The RP-HPLC acceptance criteria for Drug Product at release and on stability are revised:

<sup>(b)</sup>(4)

Specifically, the acceptance range of Peak-1&2 is changed from <sup>(b)</sup>(4) to <sup>(b)</sup>(4), and the acceptance range for Peak -6 is changed from <sup>(b)</sup>(4) to <sup>(b)</sup>(4). These changes are based on data from 125 lots of drug substance, and 51 lots of drug product. The sponsor also commits t <sup>(b)</sup>(4)

<sup>(b)</sup>(4)

*This response is acceptable. It significantly narrows down the acceptance range for Peak-1&2 and Peak-6.*

- 3) The acceptance limit for LOD is revised to NMT <sup>(b)</sup>(4)0%, the same as the bulk drug product release specification.

*The response is acceptable. The limit is consistent with the acceptance limit of bulk drug product.*

*Additional stability data should be provided when available to support the proposed shelf life. Additional stability data should cover the stability of MT12 (12 counts, 100 counts), MT18 (12 counts, 100 counts), MT20 (12 counts, 100 counts, and 500 counts).*

**FDA Comment-4:**

**You have not provided a study that addressed the stability of the product once the final container is opened by the pharmacist or by the patient. Provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.**

Response:

The sponsor conducted the following studies to assess the in-use stability:

Temperature excursion and thermo cycling studies  
Cold storage conditions at 5°C studies  
In-use stability study  
Photostability

1. Temperature excursion and thermo cycling studies:

Samples are subjected to at the beginning or near the end of shelf life are subjected to the stress conditions described below:

For the thermocycling study, samples were incubated at -20°C for 2 days and then at 25°C/60% RH for 3 days. This cycle is repeated twice.

For the high temperature excursion study, samples were stressed at 40°C/75% RH for 10 days.

The following tests were performed on the stressed samples: Description, Seal integrity, Appearance, Loss on drying, Dissolution, Lipase activity, Amylase activity, and Protease activity.

*The set of assays used by Axcan is similar to assays performed by other PEP sponsors for the in-use stability studies. These assays are acceptable for the determination of in-use product stability.*

*Axcan reported results for all three strengths studied under both conditions, at the beginning and near the end of shelf life. The differences between before and after*

*the stress treatments (thermocycling and high temperature excursions) are minimal and are within the acceptance ranges.*

*The test results demonstrate that the product is stable under temperature conditions that might be encountered when the product is handled by patients, both at the beginning and near the end of the shelf life:*

2. Cold Storage Conditions at 5°C studies:

Stabilities studies under cold storage conditions (5°C) were conducted on a total of seven batches, covering all three dosage strengths in packaged configurations. The data presented included the results of C of A from Eurand Bulk release, C of A from Axcan release, and 0, 3, 6, 9, 12, and 18 months data.

*I reviewed all data submitted by the sponsor. The results of the tests are all within specifications. No unusual changes and trending were identified.*

*The results of Lipase amylase and protease activity assays, obtained from all samples had an RSD of 4%, 7%, and 10% respectively.*

*Compared to the assay variations, this fluctuation is acceptable. The results of cold storage conditions indicate that the product is stable when maintained at low temperatures for up to 18 months.*

3. In-use stability study according to EMEA Guidance:

The purpose of this study is to demonstrate the stability of ULTRESA after the final container is opened by the pharmacist or patient and during normal use by the patient.

The sponsor estimated that MT12capsules and MT20 capsules are consumed at a rate of 6 and 16 capsules per day respectively, and that the bottles are opened 5 times per day on average. A 100 counts bottle will last 17 days, and a 500 counts bottle will last 31 days.

Axcan tested samples from two batches of MT12 (100 counts) and MT20 (500 counts) strengths. For each strength, samples at the beginning and at the end of the shelf life were selected. The latter (500 counts) is considered to represent the worst case scenario for in-use stability, because it has the longest in-use period. The 12 counts products are physician samples, and are consumed within 24 hours after opening. The in-use stability of MT18 can be reasonably bracketed.

In the study, Axcan tested MT12 bottles t = 0, 10 days and 15 days after opening, and MT20 bottles t = 0, 15 days, and 30 days after opening.

*The results of the study indicate that the differences between samples are minimal and fall within the approved acceptance range. The RSDs for enzymatic activities are all under  $\frac{(b)}{(4)}$ % except for one protease samples which has RSD of  $\frac{(b)}{(4)}$ %, however this result is within the variability of the assay ( $\sim \frac{(b)}{(4)}$ %); therefore the RSD difference is not considered significant.*

*My assessment is that under typical use conditions, this product is stable after the final package is open. This in-use stability study and result are acceptable.*

4. Photostability:

The study was conducted to provide information on the stability of the product when exposed to artificial day light outside of the container closure protection, according to ICH Q1B Photostability Testing of New Drug Substances and Products.

The sponsor selected MT12 and MT18 as the study samples. MT12 is more sensitive to stress conditions because of its smaller size, and MT18 has a more transparent capsule shell, and is likely to be more sensitive to light exposure.

MT12 and MT18 samples were exposed to NLT 1.2 million lux hours of illumination and 200 watt hours/square meter of UV energy, according to ICH Q1B. A control wrapped in aluminum foil was also included.

Comparisons were made to evaluate the difference between the samples and the control:

	Ultrase MT12, lot D090185B			Ultrase MT18, lot F090278A		
	Lipase	Amylase	Protease	Lipase	Amylase	Protease
Difference between unstressed (initial) and stressed capsules	2.1%	3.9%	-3.5%	0.9%	-1.5%	1.6%
Difference between dark control and stressed capsules	-4.8%	-1.9%	5.8%	-0.3%	2.3%	-1.5%

*I reviewed the data submitted by the sponsor. The largest differences for lipase, amylase, and protease activities are around 5%, 4%, and 6% respectively. These differences are all within assay variability. The photo stability study and data submitted indicate that the product is not sensitive to light; therefore a recommendation to protect from light is not necessary.*

**FDA Comment-5:**

**The stability data you have provided for the 12 count bottle only support a 12 month expiry. Revise your label accordingly, or provide additional data to support your requested dating period of 16 months.**

Response:

The firm agrees to revise the 12 count bottle label to a 12 month expiry until further stability data is provided to support a longer expiry date.

*Acceptable.*

**Additional Review:**

*In review of Package Insert (PI), I find that the description of the printing on capsules of each dosage strength is different from the drug product description provided in Section 3.2.P.5.1 of NDA submitted on March 26, 2010:*

<u>Drug Product</u>	<u>PI: capsule cap</u>	<u>NDA 3.2.P.5.1: capsule cap</u>
MT12	13800UL	ULTRASE
MT18	20700UL	ULTRASE
MT20	23000UL	ULTRASE

<u>Drug Product</u>	<u>PI: capsule body</u>	<u>NDA 3.2.P.5.1: capsule body</u>
MT12	AXCA	MT12
MT18	AXCA	MT18
MT20	AXCA	MT20

*Upon further investigation, I found that the information provided in DMF 15681 (drug product manufacturer) is consistent with the information in PI. Therefore, I have the following comment to the sponsor:*

**Comment:** We noted a discrepancy in the description of the capsules printing between your NDA submission and the description provided in the package insert. Please amend your NDA submission to be consistent with the information provided in the package insert.

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

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/s/

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WEI GUO  
04/30/2010

EMANUELA LACANA  
04/30/2010

BARRY W CHERNEY  
04/30/2010

**Submission:** NDA 22222  
**Product:** Ultrase<sup>®</sup> MT 12, 18, and 20 Capsules  
**Indication:** Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions  
**Formulation:** Oral, capsule, enteric coated minitablets  
**Date:** September 28, 2009  
**Sponsor:** Axcen 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:** October 5, 2009

**Recommendation:**

Send the answers to the sponsor:

The sponsor asked in the submission:

1. *In Question #4 of the Complete Response Letter, the Agency specifies "forced degradation studies". Given the TRADENAME (pancrelipase, USP) is a therapeutic protein product, stability studies are conducted under real-time, real-temperature conditions. Axcen proposes conducting the in-use studies under these conditions. Is this acceptable?*

**Answer:** No. Your proposal will address stability of the product in well-controlled conditions, but will not provide information on stability under conditions that could be encountered when the product is handled by patients. Forced degradation studies should be conducted to examine stability under unfavorable conditions and to understand the degradation pathways of the product. Please conduct forced degradation studies under stress conditions such as, but not limited to, product exposed to extremes of temperature, humidity, and light (photostability), etc. for various period of time. The results of your studies will be used to support in-use stability information provided to the patients in the package insert and medication guide.

2. *Is an in-use study,*

*a. conducted in the marketed package (white HDPE bottle),  
b. with the dessicant removed, and*

- c. *in which the bottle is stored and opened 5 times per day, with an appropriate number of capsules removed at each opening, in a well lit environment,*

*sufficient to satisfy the Agency's request (Question #4)?*

Answer: No. Please refer to our answer to Question 1.

## **CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

NDA 22-222 was first submitted in July 31, 2007. The sponsor received an "Approvable Letter on July 1, 2008, and a Complete Response Letter on September 9, 2009.

The sponsor sent a request for feedback on September 28, 2009 after receiving the Complete Response Letter dated September 9, 2009. The sponsor requested clarification on Comment #4:

"You have not provided a study that addressed the stability of the product once the final container is opened by the pharmacist or by the patient. Provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product."

The sponsor requested the Agency's feedback on the following questions:

- 1. In Question #4 of the Complete Response Letter, the Agency specifies "forced degradation studies". Given the TRADENAME (pancrelipase, USP) is a therapeutic protein product, stability studies are conducted under real-time, real-temperature conditions. Axcan proposes conducting the in-use studies under these conditions. Is this acceptable?*

In Question-1, the sponsor proposed to conduct the stability study under real-time real-temperature condition. This proposal is not acceptable. The stability data provided in this NDA are obtained at 25°C/60% RH and 30°C/65% RH, and they are not sufficient to establish a degradation profile for the drug substance. Forced degradation study should be conducted to understand the product degradation pathways and stability under stress conditions.

Answer: No. Your proposal will address stability of the product in well-controlled conditions, but will not provide information on stability under conditions that could be encountered when the product is handled by patients. Forced degradation studies should be conducted to examine stability under unfavorable conditions and to understand the degradation pathways of the product. Please conduct forced degradation studies under stress conditions such as, but not limited to,

product exposed to extremes of temperature, humidity, and light (photostability), etc. for various period of time. The results of your studies will be used to support in-use stability information provided to the patients in the package insert and medication guide.

2. *Is an in-use study,*

- a. conducted in the marketed package (white (b) (4) bottle),*
- b. with the dessicant removed, and*
- c. in which the bottle is stored and opened 5 times per day, with an appropriate number of capsules removed at each opening, in a well lit environment,*

*sufficient to satisfy the Agency's request (Question #4)?*

In Question-2, the sponsor proposed to study the in-use stability under marketed package, with dessicant removed, open and close the bottles 5 time a day. While this information is useful, it does not reflect the conditions that can be found when the product is handled by the patients, since often products are placed in conditions of temperature or humidity that have not been adequately studied. Therefore, in-use stability study should be performed under stress conditions.

Answer: No. Please refer to our answer to Question 1.

This is the end of this review.

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

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/s/  
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WEI GUO  
10/16/2009

EMANUELA LACANA  
10/16/2009

**Submission:** NDA 22222  
**Product:** Ultrase<sup>®</sup> MT 12, 18, and 20 Capsules  
**Indication:** Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions  
**Formulation:** Oral, capsule, enteric coated minitables

Review Date: July 2, 2009

Recommendation: Send the following comment to the sponsor:

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

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

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/s/

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WEI GUO  
09/08/2009

EMANUELA LACANA  
09/08/2009

BARRY W CHERNEY  
09/09/2009

**Submission:** NDA 22222  
**Product:** Ultrase<sup>®</sup> MT 12, 18, and 20 Capsules  
**Indication:** Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions  
**Formulation:** Oral, capsule, enteric coated minitables

**Date:** April 17, 2008  
**Sponsor:** Axcan Scandipharm, Inc.

**CMC Reviewer:** Wei Guo, Ph.D., HFD-122  
**Through:** Gibbes Johnson, Ph.D., HFD-122, Chief, Lab of Chemistry  
Barry Cherney, Ph.D., HFD-122, Deputy Director, DTP  
**Review Date:** May 1, 2008

**Recommendation:** **Approvable.**

**Send the following comments to the sponsor:**

- 1. We found that the DMFs supporting your application, DMF (b) (4) and DMF 15681 are deficient. Letters stating all deficiencies will be sent to the DMF holders. Please be advised that the approvability of your NDA depends on satisfactory responses from the DMF holders.**
- 2. In addition, we have the following comments:**
  - a. You have not provided real time stability data to support a 24 month expiry. Furthermore, you have reported several Out Of Specification (OOS) findings that also do not support you proposed expiry dating. All methods used in support of expiry must be validated and should not be changed during the stability studies. The stability data contained in your application are sufficient to support a dating period of 9 months for the drug product. ICH Q5C indicates that expiry dating of products in which the active components are proteins should be set using real time, real temperature stability data.**
  - b. Please provide stability data on drug product lots manufactured in 2006 and 2007. Please include trend analysis of all stability data with the 95% confidence interval. A commitment to investigate OOS or out of trend results in stability testing should be stated in the stability protocol.**
  - c. Please include tests for (b) (4) content, product-related substances and impurities (i.e. degradants) in your drug product release and stability programs.**
  - d. Due to the potential inconsistencies and reliance on USP lipase reference standard, we recommend the development and implementation of a**

**method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.**

## CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

### I. Introduction:

NDA 22-222 was submitted in July 31, 2007. The sponsor is Axcan Scandipharm, Inc.

Axcan is responsible for packaging and final drug product release.

The drug substance is manufactured by (b) (4) (DMF (b) (4)



The drug product is manufactured by Eurand S.p.A. (DMF 15681). Eurand is responsible for Drug Product manufacturing, packaging, release testing and stability of bulk Ultrase MT capsules.

Eurand S.p.A  
Via Martin Luther King, 13  
20060 Pessano con Bornago (MI)  
Italy  
Contact Name: Massimo Latino  
Europe Regulatory Affairs Director  
Tel:+39 02954281

Authorization letters are provided.

### Categorical Exclusion:

This application involves "biologic" substances, pancreatic enzymes, that occur naturally in the environment as describe in FDA Guidance Environmental Assessment of Human Drug and Biologics Applications. Approval of this supplement 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.

### II. Review:

This review is focused on CMC only.

See review of DMF (b) (4) for drug substance information. See review of DMF 15681 for drug product information.

The following CMC information is assessed in this review: Finished Product Packaging and Finished product stability.

The Axcan's stability program is to confirm the shelf life of ULTRASE® MT capsules in the commercial packaging at the intended storage condition of (b) (4) C.

The drug product manufacturer has an on-going stability program for the bulk capsules stored in (b) (4) bags. It is reviewed in DMF 15681.

### 3.2.P.1 Description and Components of the Drug Product

The components of drug product are reviewed in review of DMF No. 15681.

### 3.2.P.2 Pharmaceutical Development

This information is reviewed in review of DMF No. 15681.

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturers:

Axcan is responsible for release of the packaged ULTRASE MT capsules and overall administration of the packaged ULTRASE MT capsules stability program.

Firms involved in this NDA:

(b) (4)  
Eurand S.p.A.

The DS manufacturer, DMF (b) (4)  
The DP manufacturer, DMF 15681

**Comment:** We found that the DMFs supporting your application, DMF (b) (4) and DMF 15681 are deficient. Letters stating all deficiencies will be sent to the DMF holders. Please be advised that the approvability of your NDA depends on satisfactory responses from the DMF holders.

Other firms involved are:

Finished Product Packaging:

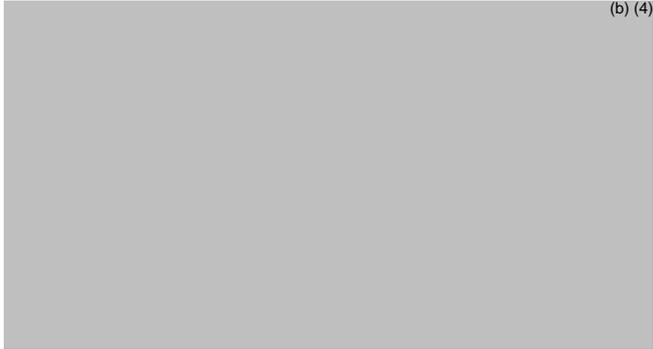
(b) (4)

(b) (4)



Packaged ULTRASE® MT capsules testing and stability testing:

(b) (4)



**3.2.P.3.3 Description of Manufacturing Process and Process Controls:**

The manufacturing process of the drug product is reviewed in DMF 15681.

Packaging Process:

Finished Product Packaging is performed by (b) (4)

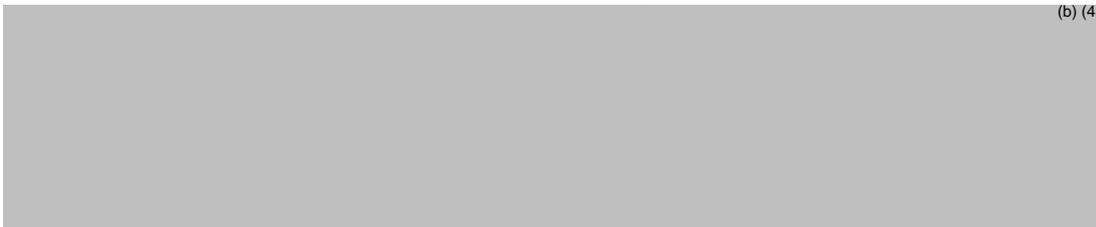
The packaging procedures are:

(b) (4)



The in-process controls are performed every (b) (4) minutes for the following parameters:

(b) (4)



**3.2.P.4 Control of Control of Excipients:**

This information is reviewed in review of DMF No. 15681.

**3.2.P.5 Control of Drug Product:**

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Wei Guo  
7/1/2008 12:52:22 PM  
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Gibbes R Johnson  
7/1/2008 01:20:45 PM  
CHEMIST

Barry Cherney  
7/1/2008 01:27:31 PM  
CHEMIST

**ONDQA Pre-Marketing Assessment Division II  
Branch III  
NDA Consultation - Quality Assessment**

1. **NDA number:** 22-222
2. **OND Division:** HFD-180
3. **Applicant Name and Address:**

Axcan Scandipharm, Inc.  
c/o CanReg Inc.  
450 North Lakeshore Drive  
Mundelein, IL 60060

4. **Drug Reviewed:** ULTRASE
5. **Purpose of Consultation:** To review the dissolution study of the drug product.

6. **Summary:** The analytical procedures used for dissolution, dissolution acceptance criteria for the drug product, and stability results for dissolution were reviewed. The dissolution trends observed during the stability studies support the proposed expiration dates. However, Pancreatin Lipase reference standard was changed at least once during the course of the stability studies and the submitted data do not fully demonstrate the necessity of this change and the need for retrospective correction of some dissolution results. This reviewer finds the dissolution part of NDA 22-222 ACCEPTABLE under the condition that that the primary quality reviewer deems the Pancreatin Lipase reference standard change and bracketing used in stability program acceptable.

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Bogdan Kurtyka, Ph.D.  
Review Chemist, Branch III  
Premarketing Assessment Division II  
ONDQA

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Date

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Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Premarketing Assessment Division II  
ONDQA

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Date

## Review notes

The drug product ULTRASE consists of a capsule filled with delayed release minitablets (enteric coated) containing Pancrelipase USP and compendial excipients. Three strengths are proposed – ULTRASE MT12 with 13,800 USP Units Lipase, ULTRASE MT18 with 20,700 USP Units Lipase, and ULTRASE MT20 with 23,000 USP Units Lipase.

The proposed containers include 100 and 500 count HDPE bottles and physician samples in 12 count HDPE bottles. The applicant proposes 24 months shelf life for 100 and 500 count bottles and 14 months shelf life for 12 count bottles.

The current review deals with all parts of NDA 22-222 related to dissolution as follows:

- analytical procedures used for dissolution,
- reference standards,
- acceptance criteria for dissolution in the drug product specification,
- conformance of registration batches to specification on release, and
- stability results for dissolution

The analytical procedure for dissolution follows the method outlined in the USP monograph on Pancrelipase Delayed-Release Capsules.

It is noted that for the calculation of the lipase activity after 30 minutes of dissolution in the phosphate buffer, a correction factor of 1.05 is used to compensate for the lipase loss of activity over the period of 30 minutes in the buffer at 37°C. This correction was implemented and validated after 6 months from the beginning of the stability program, and applied retrospectively to the dissolution results obtained by then. The value of the correction factor is supported by data documented in the method validation. ACCEPTABLE.

The applicant changed the Pancreatin Lipase reference standard (used for assay and dissolution determination) after initial and one month stability data were obtained. The new reference standard made assay and dissolution results appear higher and the existing data were retrospectively corrected. The application includes data in support of the reference standard change in Appendix A (submitted in Amendment 0011). However the Appendix A does not clearly explain why the new standard was selected over the old one. The reference standard change and supporting data are described and discussed closer in Appendix 1 at the end of this review.

Taking into consideration that Pancreatin Lipase reference standard is used in both assay and dissolution tests and its change affects results of both attributes, this section is ACCEPTABLE under the condition that that the primary quality reviewer deems the standard acceptable.

The drug product specification proposes a limit of NLT 75% (Q) in 30 minutes for dissolution. This limit is consistent with the USP monograph on Pancrelipase Delayed-Release Capsules. The application does not include multiple-point dissolution curves that normally are the basis for establishing the dissolution acceptance criteria. However, in the case of this delayed release drug product, the faster dissolution (e.g., 75% in 15 minutes) would not compromise the safety and efficacy of the drug. The drug acts locally by helping to digest fats, starches, and protein, and is not systemically absorbed. Therefore its increased levels would not create safety hazards. ACCEPTABLE.

The application includes batch analysis data for all commercial and stability drug product batches manufactured in support of the NDA, a total of 9 batches. All batches show dissolution results above limit. ACCEPTABLE.

Formal stability studies were performed using the proposed commercial container/closure system. 16 months data at long term conditions and 12 months data at intermediate conditions are provided in the application. The applicant proposes 24 months shelf life for 100 and 500 count bottles and 14 months shelf life for 12 count bottles.

Although some dissolution test went into Stage 2, all dissolution results were above the specification limit at both conditions for drug product packaged in 100 and 500 count bottles. The proposed shelf life of 24 months for 100 and 500 count bottles is supported by dissolution data. The drug product in 12 count bottles failed the dissolution test for 12 months time point at intermediate conditions. However, taking into consideration that all dissolution results for 12 count bottles were above the limit at long-term conditions, and the drug was put on stability 4 months after the manufacturing date, the proposed shelf life of 14 months for 12 count bottles is supported by dissolution data.

It is noted that the applicant uses bracketing design in the stability study. However, the analysis of stability study design and evaluation of its suitability is beyond the scope of this review.

## **Appendix 1.**

### *Discussion of Pancreatin Lipase reference standard change and supporting data.*

The information on Pancreatin Lipase reference standard included in the application is not completely clear and sometimes inconsistent.

The “16 Months Stability Data Evaluation Report” submitted in Amendment 0010 states on pages 6 and 12 that “For initial and 1-month time points, the samples have been tested against USP primary reference standard and results have been recalculated against the Eurand’s standard”. Contradicting statement appears in Appendix A (submitted in Amendment 0011): “Results for lipase and dissolution tests at the initial and 1-month time points (30°C/65%RH) and initial time point (25°C/60%RH) were initially tested using the (b) (4) secondary standard. However, review of laboratory investigation HN-257 concluded that results generated using the (b) (4) secondary standard provided significantly different results when compared to the standard used by the drug product manufacturer (Eurand standard P13309305)”.

Appendix A through the experimental data clearly shows that assay and dissolution results are about 4% higher when the Eurand’s standard is used. The application also includes Certificate of Analysis of Eurand’s standard which clearly shows that it was qualified against the USP standard. Although the application does not include the CoA for (b) (4) standard, it mentions that it was qualified (presumably also against USP primary standard).

In view of this information, the following issues arise:

- If the USP primary reference standard was used for initial and 1-month time points, why different results were obtained with the reference standard qualified against the first one.
- If the (b) (4) secondary standard was used for initial and 1-month time points, why different results were obtained with the Eurand’s standard when both were qualified against USP primary reference standard.
- The Appendix A shows that assay and dissolution results are about 4% higher when the Eurand’s standard is used. However, the included data do not indicate that the higher result is the true representation of lipase activity and the Eurand’s standard should be used.

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Bogdan Kurtyka  
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Moo-Jhong Rhee  
3/19/2008 01:31:20 PM  
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Chief, Branch III