

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-222Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

30 January 2011

NDA: 22-222/N-000

Drug Product Name

Proprietary: ULTRESA capsules

Non-proprietary: pancrelipase, USP

Review Number: 4

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
1 September 2011	1 September 2011	18 October 2010	18 October 2010

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
27 May 2010	3	30 June 2010
N/A	2	24 March 2010
31 July 2007	1	29 January 2008

Applicant/Sponsor

Name: Axcan Pharma Inc.
Address: 22 Invernes Center Parkway
Suite 310
Birmingham, AL 35242

Representative: Nicole Brufatto
Telephone: 866-722-6734

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original NDA Resubmission
 - 2. SUBMISSION PROVIDES FOR:** Microbial limits testing information
 - 3. MANUFACTURING SITE:** Eurand S.p.A
Via Martin Luther King, 13
20060 Pessano con Bornago
(MI)
Italy
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Solid capsule
 - Oral
 - Various strengths
 - 5. METHOD(S) OF STERILIZATION:** Non-sterile drug product
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment for exocrine pancreatic insufficiency.
- B. SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4)
- C. REMARKS:** The submission was provided electronically in CTD format.

filename: N022222R4.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 22-222 is recommended for approval from the standpoint of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**
Not applicable

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**
ULTRESA is a non-sterile solid oral dosage form with microbial limit specifications.
- B. Brief Description of Microbiology Deficiencies -**
No deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
Not applicable

III. Administrative

- A. Reviewer's Signature** _____
Stephen E. Langille, Ph.D.
- B. Endorsement Block** _____
Bryan Riley, Ph.D.
Team Leader
- C. CC Block**
N/A

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/s/

STEPHEN E LANGILLE
01/31/2012

BRYAN S RILEY
01/31/2012
I concur.

MEMORANDUM



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

DATE: 23 November 2010

TO: NDA 22-222/N000

FROM: Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/New Drug Microbiology Staff

THROUGH: James L. McVey
Team Leader
CDER/OPS/New Drug Microbiology Staff

cc: Elizabeth Ford – Regulatory Project Manager
DARRTS

SUBJECT: **Addendum to Quality Microbiology Review 30 June 2010**
Product: ULTRESA capsules
Sponsor: Axcan Pharma Inc.

In the quality microbiology review of NDA 22-222/N-000 dated 30 June 2010, DMF (b) (4) was found to be adequate (DMF review 08 June 2010). This finding was part of the basis for the recommendation to approve the application from a quality microbiology perspective.

The review of subsequent amendments to DMF (b) (4) resulted in a request for additional product quality microbiology information (IR dated 27 October 2010). NDA 22-222/N000 can not be recommended for approval until the product quality microbiology deficiencies cited in the 27 October 2010 information request have been adequately addressed.

END

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/s/

STEPHEN E LANGILLE
11/24/2010

BRYAN S RILEY
11/24/2010
I concur.

Product Quality Microbiology Review

30 June 2010

NDA: 22-222

Drug Product Name

Proprietary: ULTRESA capsules

Non-proprietary: pancrelipase, USP

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
27 May 2010	27 May 2010	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
31 July 2007	1	29 January 2008
N/A	2	24 March 2010

Applicant/Sponsor

Name: Axcán Pharma Inc.
Address: 22 Invernes Center Parkway
Suite 310
Birmingham, AL 35242

Representative: Nicole Brufatto
Telephone: 866-722-6734

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original NDA
 - 2. SUBMISSION PROVIDES FOR:** Microbial limits testing information
 - 3. MANUFACTURING SITE:** Eurand S.p.A
Via Martin Luther King, 13
20060 Pessano con Bornago
(MI)
Italy
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Solid capsule
 - Oral
 - Various strengths
 - 5. METHOD(S) OF STERILIZATION:** Non-sterile drug product
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment for exocrine pancreatic insufficiency.
- B. SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4)
- C. REMARKS:** The submission was provided electronically in CTD format.

filename: N022222R3.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 22-222 is recommended for approval from the standpoint of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**
Not applicable

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**
ULTRESA is a non-sterile solid oral dosage form with microbial limit specifications.
- B. Brief Description of Microbiology Deficiencies -**
No deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
Not applicable

III. Administrative

- A. Reviewer's Signature** _____
Stephen E. Langille, Ph.D.
- B. Endorsement Block** _____
Bryan Riley, Ph.D.
- C. CC Block**
N/A

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

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/s/

STEPHEN E LANGILLE
06/30/2010

BRYAN S RILEY
06/30/2010
I concur.

MEMORANDUM



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

DATE: 24-March-2010

TO: Elizabeth Ford - RPM

FROM: Stephen E. Langille, Ph.D. – Product Quality Microbiology Reviewer

THROUGH: James McVey – Microbiology Team Leader

SUBJECT: NDA 22-222

The product quality microbiology review of NDA 22-222 was completed on January 29, 2008. The review covered the manufacturing process and microbial limit specifications for the drug product manufactured at Eurand S.p.A and recommended approval from the standpoint of product quality microbiology.

As a result of a 483 issued to the drug substance manufacturer, (b) (4) (b) (4) on (b) (4) (b) (4) that cited abnormally high levels of microorganisms in the drug substance, (b) (4) DMF (b) (4) (b) (4) was reviewed. Product quality microbiology deficiencies were sent to (b) (4) in a letter dated September 15, 2009. (b) (4)'s October 21, 2009 response to these deficiencies is still under review.

The results of recent testing done by the FDA's Southwest Regional Lab show that one of seven drug substance samples obtained from (b) (4) was positive for *Bacillus cereus* enterotoxin. Because of this, I recommend that each lot of drug substance manufactured at (b) (4) have a release specification for the absence of *B. cereus* enterotoxin. This recommendation is based upon the following:

1. One of the seven samples of drug substance obtained from (b) (4) has tested positive for the presence of *B. cereus* enterotoxin. It's not clear if the presence of the toxin in this sample is an aberration or a common event.
2. Subject matter experts at CDER and CFSAN agree that the presence of *B. cereus* enterotoxin in Pancrelipase drug product could result in significant gastrointestinal adverse events or systemic illness, particularly in immunocompromised patients.
3. (b) (4) (b) (4) could be responsible for *B. cereus* growth and toxin production during drug substance processing. Further, (b) (4) (b) (4) employed at (b) (4) may allow the heat labile toxin to survive processing.

MEMORANDUM

4. The drug product manufacturing process does not appear to include [REDACTED] (b) (4) [REDACTED].
5. (b) (4) has been reluctant to address the product quality deficiencies identified in the Drug Master File.

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

The Office of Compliance is currently working with (b) (4) on methods to control the presence of *B. cereus* enterotoxin in the drug substance. Information covered in this memo, will be conveyed to (b) (4) through the Office of Compliance in order to improve the overall microbiological product quality of the drug substance.

END

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/

STEPHEN E LANGILLE
03/26/2010

JAMES L MCVEY
03/29/2010
I concur.

Product Quality Microbiology Review

29-January-2008

NDA 22-222

Drug Product Name

Proprietary: ULTRASE® MT12, ULTRASE® MT18,
ULTRASE® MT20 Capsules

Non-proprietary: Pancrelipase, USP

Drug Product Priority Classification: Priority

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
7/31/07	8/1/07	N/A	N/A
12/20/07	12/21/07	N/A	N/A
1/21/08	1/23/08	N/A	N/A

Submission History (for amendments only): Not applicable

Applicant/Sponsor

Name: Axcan Pharma Inc.
Address: 22 Invernes Center Parkway
Suite 310
Birmingham, AL 35242

Representative: Sophie Tanguay
Regulatory Affairs
CanReg, Inc.

Telephone: 866-722-6734

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original submission
 2. **SUBMISSION PROVIDES FOR:** Microbial limits testing information
 3. **MANUFACTURING SITE:** Eurand S.p.A
Via Martin Luther King, 13
20060 Pessano con Bornago (MI)
Italy
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Solid capsule
 - Oral
 5. **METHOD(S) OF STERILIZATION:** Non-sterile drug product
 6. **PHARMACOLOGICAL CATEGORY:** Treatment for exocrine pancreatic insufficiency.
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** NDA 22-222 was submitted in eCTD format. There was no initial quality assessment in DFS. The applicant provided amendments to the NDA on December 20, 2007 and January 21, 2008 in response to product quality microbiology information requests.

filename: N022222R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 22-222 is recommended for approval from the standpoint of a satisfactory product quality microbiology review.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –**
Not applicable

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**
The drug product is a dry solid oral dosage form derived from porcine pancreas. Microbial limits specifications have been established based upon compendial recommendations.
- B. Brief Description of Microbiology Deficiencies -**
No product quality microbiology deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
Not applicable

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
James McVey – Team Leader
- C. CC Block**
N/A

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/s/

Stephen Langille
1/29/2008 08:59:27 AM
MICROBIOLOGIST

James McVey
1/29/2008 09:24:31 AM
MICROBIOLOGIST

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-222

Applicant: Axcan Pharma

Letter Date: 9/28/07

Drug Name: Ultrase

NDA Type: Priority

Stamp Date: 9/28/07

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?			The drug product is not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			No such data or studies were requested
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The microbial limits proposed by the applicant exceed those suggested in the current edition of the United States Pharmacopeia. The applicant should be advised of this and asked to lower the specifications to meet compendial specifications.

Stephen E. Langille, Ph.D.

Date

David Hussong, Ph.D.

Date

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/s/

Stephen Langille
11/19/2007 11:15:19 AM
MICROBIOLOGIST

David Hussong
11/19/2007 11:20:24 AM
MICROBIOLOGIST