CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022535Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

13 August 2014

NDA: 22-535/ SD-050 (Class 2 Resubmission)

Drug Product Name
Proprietary: Esbriet
Non-proprietary: Pirfenidone Capsule

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
23 May 2014	23 May 2014	19 June 2014	20 June 2014

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
04 November 2009 29 January 2010 05 March 2010 05 April 2010	1 2	23 March 2010 28 April 2010

Applicant/Sponsor
Name: InterMune Inc.
Address: 3280 Bayshore Boulevard
Bisbane, CA 94005
Representative: James L'Italien, Ph.D., Senior VP Regulatory Affairs and Quality Assurance
Telephone: 415-723-7643

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(1) (Class 2 Resubmission)

2. SUBMISSION PROVIDES FOR: Responses to the Complete Response Letter dated 04 May 2010

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Capsule, Oral administration, 267mg potency

5. METHOD(S) OF STERILIZATION: Not Applicable

6. PHARMACOLOGICAL CATEGORY: Treatment of idiopathic pulmonary fibrosis (IPF)

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology reviews #1 and #2, dated 23 March 2010 and 28 April 2010, respectively (J. McVey).

C. REMARKS: The current review addresses the microbiology deficiencies listed in the Complete Response Letter dated 04 May 2010.

filename: N22535N000R3.docx

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Microbial limits testing is part of the release testing program. The CR Letter cited issues with the sample size used in the assay. The Applicant has responded by modifying the method to permit an increase in sample size for analysis.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – Not Applicable.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block _____
Neal J. Sweeney, Ph.D.
Senior Microbiology Reviewer

C. CC Block: NDA 22535

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/s/

ROBERT J MELLO
08/14/2014

NEAL J SWEENEY
08/14/2014
I concur.

Product Quality Microbiology Review

28 April 2010

NDA: 22-535/N-000 Amendment 0035

Drug Product Name
Proprietary:
Non-proprietary: Pirfenidone Capsule

Review Number 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
4/5/2010	4/5/2010		

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
11/4/09 1/29/10 3/5/10	1	3/25/10

Submission History (for amendments only). N.A.

Applicant/Sponsor

Name: InterMune Inc.
Address: 3280 Bayshore Boulevard
Bisbane, CA 94005
Representative: Marianne Armstrong, PhD
Telephone: (415) 466-2532

Name of Reviewer: James L. McVey

Conclusion: This is a review of a response to an information request letter. See the microbiologist's comments at the end of this review.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** New NDA – Orphan Drug Status granted 3/5/04.

2. **SUBMISSION PROVIDES FOR:** A response to the information request.

3. **MANUFACTURING SITE:**

(b) (4)

[redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** capsule

5. **METHOD(S) OF STERILIZATION:** Not sterile.

6. **PHARMACOLOGICAL CATEGORY:** An antifibrotic agent for treatment of pulmonary fibrosis.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** The consult requests a microbiology review of the Methods Package for Microbial Limits testing. This is a review of a response to an information request letter. See the microbiologist's comments at the end of this review.

filename: n22353r2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – An information request is recommended.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N.A.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - N.A.

B. Brief Description of Microbiology Deficiencies –See questions with responses in section 1 below.

C. Assessment of Risk Due to Microbiology Deficiencies – Although all data so far indicate that the product lots test at below the limit of detection for the assay selected, there is no evidence that the limit of detection selected is sufficient. The risk to human health is low because most yeasts and molds present would be in low numbers. The claim to detect (b) (4) cfu/mL in a sample diluted (b) (4) is not likely to succeed, but (b) (4) cfu/mL would be detected. Therefore the product would have a titer of < (b) (4) cfu of yeasts and mold, the same as for bacteria. However, if pathogens were present that were resistant to the antimicrobial effect of this drug, the limit of detection for these tests may not be adequate to assure patient safety. A filtration method that tests a larger sample is more appropriate for this product.

III. Administrative

A. Reviewer's Signature _____
James L. McVey

B. Endorsement Block _____
Microbiology Supervisor David Hussong, PhD

C. CC Block
N22535r1.doc

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

JAMES L MCVEY
04/30/2010

DAVID HUSSONG
05/03/2010
I concur that the microbial limits assay method is inadequate. The applicant needs to correct or explain the method.

Product Quality Microbiology Review

23 March 2010

NDA: 22-535/N-000

Drug Product Name
Proprietary:
Non-proprietary: Pirfenidone Capsule

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
11/4/09	11/4/09	2/17/10	2/24/09
1/29/10	1/29/10		
3/5/10	3/5/10		

Submission History (for amendments only). N.A.

Applicant/Sponsor
Name: InterMune Inc.
Address: 3280 Bayshore Boulevard
Bisbane, CA 94005
Representative: Marianne Armstrong, PhD
Telephone: (415) 466-2532

Name of Reviewer: James L. McVey

Conclusion: Please send an information request letter. See the microbiologist's comments at the end of this review.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** New NDA – Orphan Drug Status granted 3/5/04.

2. **SUBMISSION PROVIDES FOR:** The CMC section is included in this complete submission. .

3. **MANUFACTURING SITE:**

(b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** capsule

5. **METHOD(S) OF STERILIZATION:** Not sterile.

6. **PHARMACOLOGICAL CATEGORY:** An antifibrotic agent for treatment of pulmonary fibrosis.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** The consult requests a microbiology review of the Methods Package for Microbial Limits testing.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending resolution of microbiology issues. See comments at end of review.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N.A.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - N.A.

B. Brief Description of Microbiology Deficiencies – The examination of the selection of the methods used for determining the microbial limits of the product are unclear.

C. Assessment of Risk Due to Microbiology Deficiencies – Although all data so far indicate that the product lots test at below the limit of detection for the assay selected, there is no evidence that the limit of detection selected is sufficient. The risk to human health is low because most microflora would be below (b) (4) cfu/gram. However, if pathogens were present, then the limit of detection for these tests may not be adequate to assure patient safety.

III. Administrative

A. Reviewer's Signature _____
James L. McVey

B. Endorsement Block _____
Microbiology Supervisor David Hussong, PhD

C. CC Block
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

JAMES L MCVEY
03/24/2010
Information request needed.

DAVID HUSSONG
03/25/2010
I concur with the reviewer's request for additional information.