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RESEARCH**

APPLICATION NUMBER:

202971Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

15 FEB 2013

NDA: 202-971

Drug Product Name

Proprietary: Abilify Maintena

Non-proprietary: Aripiprazole

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
31 AUG 2012	31 AUG 2012	31 AUG 2012	06 SEP 2012
23 OCT 2012	23 OCT 2012	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
Multiple	1	19 JUL 2012

Applicant/Sponsor

Name: Otsuka Pharmaceutical Company, Ltd.

Address: 2-9 Kanda Tsukasa-cho
Chiyado-ku Tokyo, 101-8535 Japan

Representative: David Goldberger

Telephone: 609-524-6797

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Class 2 Resubmission
 - 2. SUBMISSION PROVIDES FOR:** Resubmission of an original 505(b)1 NDA.
 - 3. MANUFACTURING SITE:**
Drug Substance
Otsuka Pharmaceutical Co., Ltd.
Second Tokushima Factory
224-18, Hiraishi Ebisuno, Kawauchi-cho
Tokushima-shi, Tokushima 771-0182, Japan

Drug Product
Otsuka Pharmaceutical Co. Ltd
Tokushima Wajiki Factory
306-2 Aza Otsubo, Koniu, Naka-cho
Naka-gun, Tokushima 771-5209, Japan
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Lyophilized powder for injection supplied with or without a vial of sterile water for injection and associated syringe components (b) (4)
 - Intramuscular depot of a suspension for extended release
 - 400 mg and 300 mg/vial
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
processing of sterile drug substance and sterile excipients
 - 6. PHARMACOLOGICAL CATEGORY:** Maintenance treatment of schizophrenia
- B. SUPPORTING/RELATED DOCUMENTS:** Microbiology Review #1 dated 19 July 2012. Microbiology review of DMF (b) (4) dated 15 February 2013.
- C. REMARKS:** This submission was in the eCTD format. There were no outstanding deficiencies from Review #1 but the resubmission proposes an alternate supplier of the sterile water for injection. The microbiology review of DMF (b) (4) found the DMF adequate to support approval of this NDA.

filename: N202971R2.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – Recommended for approval.
- 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 substance approved for the Abilify oral tablet is sterilized (b) (4)
The sterile powdered drug substance (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – Not applicable.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.
- D. **Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. **Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. **Endorsement Block** _____
John Metcalfe, PhD
Senior Microbiology Reviewer
- C. **CC Block**
N/A

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/s/

JESSICA COLE
02/19/2013

JOHN W METCALFE
02/19/2013
I concur.

Product Quality Microbiology Review

18 JUL 2012

NDA: 202-971

Drug Product Name

Proprietary: Abilify Maintena

Non-proprietary: Aripiprazole

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
26 SEP 2011	26 SEP 2011	24 OCT 2011	24 OCT 2011
09 NOV 2011	09 NOV 2011	N/A	N/A
21 DEC 2011	21 DEC 2011	N/A	N/A
22 MAR 2012	22 MAR 2012	N/A	N/A
28 MAR 2012	29 MAR 2012	N/A	N/A
25 MAY 2012	25 MAY 2012	N/A	N/A
13 JUN 2012	13 JUN 2012	N/A	N/A
29 JUN 2012	29 JUN 2012	N/A	N/A
18 JUL 2012	18 JUL 2012	N/A	N/A

Applicant/Sponsor

Name: Otsuka Pharmaceutical Company, Ltd.

Address: 2-9 Kanda Tsukasa-cho
Chiyado-ku Tokyo, 101-8535 Japan

Representative: David Goldberger

Telephone: 609-524-6797

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: This NDA is recommended for approval.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** 505(b)1 NDA
2. **SUBMISSION PROVIDES FOR:** New drug product
3. **MANUFACTURING SITES:**
Drug Substance
Otsuka Pharmaceutical Co., Ltd.
Second Tokushima Factory
224-18, Hiraishi Ebisuno, Kawauchi-cho
Tokushima-shi, Tokushima 771-0182, Japan

(b) (4)

Reviewer's Comment: This site was pulled from the NDA and is no longer an alternate sterilization site for the drug substance.

Drug Product

Otsuka Pharmaceutical Co. Ltd
Tokushima Wajiki Factory
306-2 Aza Otsubo, Koniu, Naka-cho
Naka-gun, Tokushima 771-5209, Japan

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Lyophilized powder for injection supplied with or without a vial of sterile water for injection and associated syringe components (b) (4)
 - Intramuscular depot of a suspension for extended release
 - 400 mg and 300 mg/vial
5. **METHOD(S) OF STERILIZATION:** (b) (4)
processing of sterile drug substance and sterile excipients
6. **PHARMACOLOGICAL CATEGORY:** Maintenance treatment of schizophrenia
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4) is referenced for the (b) (4) drug substance manufacturing process and was found inadequate in the Microbiology Review dated (b) (4). The NDA holder withdrew the (b) (4) site in an amendment dated 18 July 2012. DMF (b) (4) contains information on the sterile vial (b) (4) and was found adequate in the Microbiology Review dated 15 June 2012.

- C. **REMARKS:** This submission was in the eCTD format. The following comments were sent in the 74-day letter and a response was received on 21 December 2011. The responses have been incorporated into the relevant sections of this review.

Request for the 74-day letter:

1. Submit the protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product (i.e., (b) (4)). For more information see the (b) (4) Guidance which can be found at the following location: (b) (4)

2. The storage of reconstituted drug product should be not more than (b) (4) at room temperature or not more than (b) (4) under refrigeration. Please revise the label or provide studies which demonstrate that low levels of inoculated microorganisms will not proliferate under the labeled storage conditions. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than (b) (4) at room temperature.

The following information request was sent to the applicant on 21 February 2011 and a response was received on 29 March 2012. The responses have been incorporated into the relevant sections of this review.

Microbiology Comment:

Provide the following information or a reference to its location.

Convenience Kit

1. Confirm that all 510k devices included in the convenience package were cleared as apyrogenic, sterile devices by CDRH. A representative certificate of analysis for each device component which indicates adequate sterility and endotoxin information would be acceptable. Alternately, provide complete sterilization (b) (4) information on each device in the convenience kit.

Sterile Drug Substance

1. Confirm that no more than 3 batches of sterile drug substance will be manufactured in a campaign.
2. Indicate how, and at what location, (b) (4) validation studies were sterilized.
3. Define the solution used for the (b) (4) during production. The established minimum (b) (4) should be supported by data presented in Module 3.2.S.2.5 Appendix B, sponsor Table 6 in document ASL200907RE.
4. Module 3.2.S.2.5 Appendix B, sponsor Table 6 in document ASL200907RE states that the maximum contact time for the challenge studies was (b) (4). The proposed maximum contact time for production is (b) (4). Confirm that the data in Table 6 is an error or provide a justification for the submitted validation studies.
5. Also in reference to Module 3.2.S.2.5 Appendix B sponsor Table 6 in document ASL200907RE, provide additional information on footnote 22 which states "It confirmed that (b) (4) on appendix photograph were not test organisms by observation." No photographs were included in the submission and it is unclear how growth on all three (b) (4) was determined to be an acceptable test result during these sterilization validation studies. We note that (b) (4) studies were conducted at a separate location from challenge studies.
6. Provide additional information on the transfer of sterile product from the (b) (4) for filling. Indicate how (b) (4) is conducted and controlled for the primary batch and for campaign batches 2 and 3.

7. Provide a description of the media and incubation conditions for detection of viable organisms in the environmental monitoring program.
8. Provide the parameters used for (b) (4) for routine production and during validation studies.
9. Provide data to support the adequacy of nutrient growth medium to be used for environmental monitoring after inclusion in the (b) (4).
10. Provide the name of the contract manufacturer used to (b) (4). Provide a summary of the validation studies which include a description of the validated loading pattern or maximum load, as applicable.
11. Provide additional information on the (b) (4) processing simulations.
 - a. Provide the acceptance criteria.
 - b. Describe how (b) (4).
 - c. Provide a justification for not packaging all (b) (4).
 - d. Provide additional clarification on what happens to the excess (b) (4) that does not get packaged as part of the simulation.
 - e. Provide the results from growth promotion testing conducted on media-filled units.
 - f. Indicate the frequency of (b) (4) processing simulations.
12. Indicate how much drug substance is packaged into each bag.
13. Provide a more detailed summary of the sterility test. In the summary please provide the solvent, the volume of media used and confirm that the sample size for the sterility test is (b) (4) containers.
14. Explain the growth promotion test results from Table 3.2.S.2.5.8-1. Indicate why the growth promotion test results were negative for both test controls.
15. Provide a more detailed summary of the endotoxin test method. Indicate what the limit of detection (lowest dilution) for the assay is.
16. Provide the supplier for the (b) (4) bags used for drug substance packaging at Otsuka.

Drug Product

1. Describe the (b) (4) product from the (b) (4) for filling.
2. Provide a justification for placing lyophilizers (b) (4).
3. Describe the (b) (4) steps used to add the sterile drug substance to the sterile vehicle solution. Indicate the level of personnel involvement and provide a description of how sterility is maintained.
4. Define (b) (4) used for vehicle (b) (4) validation studies conducted by (b) (4). Provide a comparison of the viscosity and osmolarity as compared to the vehicle.
5. The failure to include biological indicators to verify the adequacy of the sterilization (b) (4) is a concern. Provide additional information on what attempts have been made to include a (b) (4) or what other sterilization methods have been investigated which might allow for inclusion of a (b) (4).

The following information request was sent to the applicant on 24 April 2012 and a response was received on 25 May 2012. The responses have been incorporated into the relevant sections of this review.

1. As mentioned previously, we are concerned about the lack of (b) (4) efficacy data for the sterilization validation studies for the (b) (4). Please provide the following information.
 - a. Please provide a detailed diagram of the equipment and the monitoring locations.
 - b. Describe how the monitoring locations were chosen and provide information that supports the adequate (b) (4).
 - c. Provide the time and temperature results used to calculate the F₀ values in Table 5 from (b) (4) Line after the modification.
 - d. Provide a justification for not including a monitoring point in the (b) (4) in (b) (4) validation runs. We note that in (b) (4)

- studies was demonstrated to be the (b) (4).
- e. Provide a justification for not increasing the (b) (4)
- f. Provide any data from studies conducted with (b) (4)
2. Provide the results from three sterilization validation studies (b) (4)
3. Provide a summary of the results from the (b) (4)
4. Provide the (b) (4)
5. Provide the media and incubation conditions for the drug product environmental monitoring program at the (b) (4).

The following information request was sent to the applicant on 04 June 2012 and a response was received on 13 June 2012 and 29 June 2012. The responses have been incorporated into the relevant sections of this review.

Microbiology Comment:

We have the following follow-up comments after review of the 25 May 2012 amendment.

1. We note that you now plan to validate the (b) (4). Provide the results from three successful (b) (4) validation studies (b) (4) as described in the 25 May 2012 submission. If these studies are not complete provide a date when the agency can expect to receive the results from these studies.
2. Confirm that the maximum (b) (4) at the (b) (4) is the only proposed loading pattern.
3. As requested previously, provide the results from (b) (4). We note that you provided performance qualification and routine production parameters in the 25 May 2012 amendment.
4. The (b) (4)
Provide a justification for your proposed equation.

filename: N202971R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This NDA is recommended for approval on the basis 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** – The drug substance approved for the Abilify oral tablet is sterilized (b) (4)
The sterile powdered drug substance (b) (4)
- B. Brief Description of Microbiology Deficiencies** – Not applicable.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. Endorsement Block** _____
Bryan Riley, PhD
Microbiology Team Leader
- C. CC Block**
N/A

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/s/

JESSICA COLE
07/18/2012

BRYAN S RILEY
07/19/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 202-971 **Applicant:** Otsuka **Letter Date:** 26 September 2011
 Pharmaceutical Company, Ltd.

Drug Name: Aripiprazole **NDA Type:** 505(b)1 **Stamp Date:** 26 September 2011
 (extended release)

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		A type II DMF is referenced for the sterile drug substance manufacturing process. Need the DMF number.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	Summaries of the results were submitted but no protocols or detailed information were provided. See Table 3.2.P.3.5.2.10-1.
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?	X		
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?	X		
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This is an extended release formulation for intramuscular depot and uses the same active ingredient as the originally approved oral formulation for treatment of schizophrenia under NDA 21-713. This NDA submission was previously covered under IND

67,380. This product will be presented as a 300 mg and 400 mg vial for injection and as an injectable vial kit. The convenience kit will include a (b)(4) vial of Sterile Water for Injection to be used for reconstitution, a 3 mL sterile syringe with a 21 gauge needle for reconstitution, a sterile syringe without needle, one 1.5 inch and one 2 inch 21-gauge sterile safety needle for injection and a sterile vial adapter, The NDA contains letters of authorization for the device components which are all sterile and non-pyrogenic. The drug substance is a sterile (b)(4) product and a letter of authorization to a currently unnumbered DMF was provided. (b)(4)

Request for the 74-day letter:

1. Submit the protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product (i.e., (b)(4) etc). For more information see the (b)(4)

Guidance which can be found at the following location:

2. The storage of reconstituted drug product should be not more than (b)(4) at room temperature or not more than (b)(4) under refrigeration. Please revise the label or provide studies which demonstrate that low levels of inoculated microorganisms will not proliferate under the labeled storage conditions. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than (b)(4) at room temperature.

11/16/11

Jessica G. Cole
Reviewing Microbiologist

Date

11/17/11

Stephen Langille
Microbiology Secondary Reviewer

Date

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/s/

JESSICA COLE
11/18/2011

STEPHEN E LANGILLE
11/18/2011