

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206488Orig1s000**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

12 January 2016

**NDA:** 206-488/N000

**Drug Product Name**

**Proprietary:** EXONDYS 51™

**Non-proprietary:** eteplirsen

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
20 May 2015	20 May 2015	27 May 2015	03 June 2015
16 September 2015	16 September 2015	NA	NA

**Submission History (for 2<sup>nd</sup> Reviews or higher) – NA**

**Applicant/Sponsor**

**Name:** Sarepta Therapeutics, Inc.

**Address:** 215 First Street  
Cambridge MA 02142

**Representative:** Shamim Ruff  
Vice President, Regulatory Affairs and Quality

**Telephone:** (617) 274-4000

**Name of Reviewer:** Denise A. Miller

**Conclusion:** Recommended for Approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original Application
  2. **SUBMISSION PROVIDES FOR:** The manufacture and marketing of a new drug product.
  3. **MANUFACTURING SITE:**  
[REDACTED] (b) (4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Dosage Form: Sterile solution for infusion
    - Route of Administration: Intravenous infusion
    - Strength/Potency: 50 mg/mL
  5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- DMF [REDACTED] (b) (4) Type V Drug Master File, [REDACTED] (b) (4). Letter of Authorization dated April 10, 2015. Reviewed by Division of Microbiology Assessment on 12 January 2015 and was adequate.
- DMF [REDACTED] (b) (4) Type V Drug Master File, [REDACTED] (b) (4) Letter of Authorization dated April 16, 2015 [REDACTED] (b) (4) [REDACTED] (b) (4) submission dated April 8, 2014 for BER Validation. Reviewed by Division of Microbiology Assessment on 25 August 2015 and was adequate.
- DMF [REDACTED] (b) (4) Type V Drug Master File, [REDACTED] (b) (4) [REDACTED] (b) (4). Letter of Authorization: Dated April 16, 2015 to access the 08 April 2014 Amendment for the [REDACTED] (b) (4) [REDACTED] (b) (4) study. Reviewed by Division of Microbiology Assessment on 07 July 2015 and was adequate.
- C. **REMARKS:**  
This drug product has an orphan designation (07-2484)

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** - Recommended for approval based on the information provided.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** - NA

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The subject drug product is compounded (b)(4) and filled into the primary container closure (b)(4) under ISP Class 5 conditions.
- B. Brief Description of Microbiology Deficiencies** – No deficiencies was identified in the information provided.
- C. Contains Potential Precedent Decision(s)**-  Yes  No

**III. Product Quality Microbiology Risk Assessment**

**A. Initial Product Quality Microbiology Risk Assessment**

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O <sup>(3, 4, 5)</sup>	Severity of Effect (S)	Detect. (D)	Risk Priority Number <sup>6</sup> (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b)(4)						Ensure system is closed
E	(b)(4)						

**B. Final Risk Assessment** – The risk to the product for microbial and endotoxin contamination has been minimized through validation and process control.

**IV. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_  
Denise A. Miller  
Sr. Microbiologist, OPF/DMA/Branch II

**B. Endorsement Block** \_\_\_\_\_  
Neal J. Sweeney, Ph.D.  
Sr. Microbiologist, OPF/DMA/Branch II

**C. CC Block**  
N/A

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**REVIEWER COMMENT** – The stability program is acceptable from a quality microbiology perspective.

**A APPENDICES - NA**

**R REGIONAL INFORMATION**

**R.1 Executed Batch Record**

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)**

## MODULE 1

- A. PACKAGE INSERT** - Product is diluted in 100 – 150 ml sodium chloride 0.9% Injection, USP. Label states that the diluted product must be used within 4 hours. If immediate use is not possible, the diluted product may be stored for up to 24 hours at 2-8°C. All unused EXONDYS 51 is to be discarded.

### ADEQUATE

**REVIEWER COMMENT** – The proposed labeling conforms to the conditions that were discussed with the sponsor in the 17 October 2013 sponsor meeting. These proposed storage conditions are within current expectations for diluted product in the absence of supportive data.

### 3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There were no quality microbiology deficiencies identified in the information provided.

**Reviewer's Signature** Denise Miller -S  
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 Date: 2016.01.26 14:49:47 -05'00'

Denise A. Miller  
 Sr. Microbiologist, OPF/DMA/Branch II

**Endorsement Block** S  
Digitally signed by Neal J. Sweeney -S  
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 ou=People,  
 o=9.2342.19200300.100.1.1=1300109587, cn=Neal  
 J. Sweeney -S  
 Date: 2016.01.26 15:33:06 -05'00'

Neal J. Sweeney, Ph.D.  
 Sr. Microbiologist, OPF/DMA/Branch II

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 206-488      **Applicant:** Sarepta Therapeutics **Letter Date:** 26 June 2015

**Drug Name:** EXONDYS 51      **NDA Type:** 505 (B)(1)      **Stamp Date:** 26 June 2015

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
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?	√		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	√		References manufacturing DMF (b) (4) validation study was provided.
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?		√	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	√		Not preserved CCI by microbial and dye ingress. See additional comment #5
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		Sterility and endotoxin testing and specifications were provided.
7	Has the applicant submitted the results of analytical method verification studies?	√		See Additional Comment #4
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	NA		
9	If sterile, are extended post-constitution and/or post-dilution hold time in the draft labeling supported by microbiological data?		√	See Additional comment #2.
10	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:

- 1) EXONDYS 51 is designated as an orphan drug for the treatment of Duchenna muscular dystrophy in patients who have a confirmed mutation of the DMF gene that is amenable to exon 51 skipping. The dose is 30 mg/kg, (b) (4) administered intravenously over (b) (4) – 60 minutes once per week. This is a lifetime treatment. The dose of 30 mg/kg requires multiple vials to be combined for an adult dose; (b) (4)
- 2) Post dilution storage times provided on the label are within the current storage limits that are recommended in the absence of supporting data. The label lists to use the diluted product immediately. If stored, the product may be stored at 2-8°C for not more than 24 hours. (Type B meeting minutes dated 17 Oct. 2013).
- 3) DMF (b) (4) was referenced for stopper endotoxin reduction validation studies and DMF (b) (4) was referenced for the stopper sterilization. DMF (b) (4) was referenced for the manufacturing process at the contract manufacturer. Letters of Authorizations to these DMFs were provided.
- 4) Method suitability reports for the sterility and endotoxin testing were not provided. These will be requested in the 74 day letter.
- 5) The container closure integrity tests submitted in the NDA were summaries of both microbial ingress and dye ingress testing methods that were performed. The summaries were brief and missing some details. A copy of the reports will be requested in the 74 day letter.

Information Request:

- 1) As stated in the submission, the sterility testing method suitability testing has been completed but was not included. Provide either a detailed summary of the test and the results or provide a copy of the report.
- 2) As stated in the submission, the endotoxin testing method suitability testing has been completed but was not included. Provide either a detailed summary of the test and the results or provide a copy of the report.
- 3) The container closure integrity testing that was provided was a brief summary of the testing for both the dye ingress and microbial ingress testing. The summary omitted information that is needed to determine the validity of the test. Provide the following:
  - a. For the microbial ingress test:
    - i. Was the testing performed on product filled vials or on media filled vials?
    - ii. Provide a description of the positive controls.
  - b. For the dye ingress test:
    - i. Was the testing performed on product vials or on media filled vials?
    - ii. Provide a description of the positive controls.
    - iii. What is the detection method for detecting dye ingress, visual or spectrophotometric?
    - iv. What is the limit of detection?

Denise Miller -A

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cn=Denise Miller -A, 0.9.2342.19200300.100.1.1=2000286872  
Date: 2015.07.27 10:22:09 -0400

Denise A. Miller, Microbiologist

Date

Neal J. Sweeney -A

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Date: 2015.07.27 10:59:14 -0400

Neal J. Sweeney, Ph.D.

Date