

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206488Orig1s000**

**CHEMISTRY REVIEW(S)**



IND/BLA/NDA: IND 077429/ NDA 206488  
TO: Billy Dunn, M.D. (Director, Division of Neurology Products/ODE1)  
FROM: Ashutosh Rao, Ph.D. (Laboratory Chief, DBRR III/OBP/OPQ/CDER)  
THROUGH: Amy Rosenberg, M.D. (Director, DBRR III/OBP/OPQ/CDER)  
Steven Kozlowski, M.D. (Director, OBP/OPQ/CDER)  
SUBJECT: Review of dystrophin bioassays observed during inspection and related study report SR-CR-16-003  
SPONSOR: Sarepta Therapeutics  
PRODUCT: Eteplirsen (EXONDYS 51) is a phosphorodiamidate morpholino oligomer designed to bind to exon 51 of the human dystrophin pre-mRNA and intended to cause skipping of exon 51 to generate an internally truncated dystrophin protein. It is supplied as a 2 mL vial containing 100 mg (50 mg/mL) and single use 10 mL vial containing 500 mg (50 mg/mL) preservative –free solution.  
INDICATION: For the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed gene mutation amenable to exon 51 skipping.  
ROUTE OF ADMIN. Intravenous (IV) infusion  
CLINICAL DIVISION: Division of Neurology Products (ODE1/OND/CDER)

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**Executive Summary:**

*The conduct of the western blotting procedure for the biopsy samples from study 4658-301 appeared to be within the scope of the sponsor's predetermined standard operating protocol SR-CR-16-003. The inspection confirmed technical compliance with the methodology, verified sample blinding throughout the procedure, confirmed that the procurement and analysis of raw data with passing acceptance criteria was used for % dystrophin calculations and successfully verified the same data in the study report '4658-301 Week 48 Interim Analysis' submitted to the agency.*

*The Sponsor could improve upon the robustness of the detection portion of the method by adopting automated and digitized detection systems and reference standards with lower variability in the future.*

**Background:**

A limited, high-priority PDUFA inspection of a Sponsor's Laboratory Testing Site at Corvallis, OR, was conducted between June 20-24, 2016, upon request from the Division of Neurology Products, and per FACTS assignment # 11648400. The inspection assignment requested observation of the laboratory's conduct of a western blotting analytical procedure, real time confirmation of the integrity of the associated data generated from the procedure, as well as an assessment of the firm's adherence to their predefined protocols and blinding procedures. This inspection and the laboratory's performance of the western blotting procedures are associated with the Sponsor's study protocol 4658-301 (PROMOVI) titled, "An Open-Label, Multi-Center, 48-Week Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy". The study is being conducted under IND # 077429, in support of Sarepta Therapeutics, Inc.'s New Drug Application (NDA) # 206488. The inspection was conducted by myself and Young Moon Choi, Ph.D. (Lead Pharmacologist,

OSIS), and Mark Babbit (Investigator, ORA). This summary provided in this memo and requested by the Division of Neurology Products specifically addresses the dystrophin analytical aspects observed on site by me and a review of the report submitted by the Sponsor on 6/27/2016 based on the data obtained during inspection. The inspection did not include an assessment of Good Laboratory Practices or current Good Manufacturing Practices. Please refer to the Establishment Inspection Report (EIR) under the FEI number 3009712573 for a full description of the inspectional items.

For this purposes of this memo, the term ‘observation’ refers to the observed activities related to the bioassay method and not an objectionable compliance action. No objectionable FDA Form 483 observations were issued to the Sponsor. The first part of this memo summarizes the observations made during inspections regarding the control samples, western blotting procedure, dystrophin quantitation, and data analysis. The second part of the memo describes concurrence with the data set provided in study report SR-CR-16-003. It does not address the clinical efficacy or review the clinical interpretation of the % dystrophin values reported.

**1. Summary of inspectional findings at Sarepta’s Corvallis, OR, Laboratory Testing Site that conducted an interim dystrophin analyses of biopsy samples from study 4658-301 (PROMOVI) by western blot:**

The finalized western blotting protocol SR-CR-16-003 and its appendices were used as a reference during the observation of the analytical procedure with samples from study 4658-301.

*The control samples:* The normal control NC-5 was originally designated as C14-23 and obtained from (b) (4) tissue bank (b) (4) NC-5 was obtained from the biceps of a 14 year old male at (b) (4) and as per the specimen report provided by the Sponsor, which noted that this subject had no pathological diagnosis. The sample NC-5 (b) (4) was used with the week 180 samples from study 202. (b) (4)

(b) (4) The untreated DMD controls were obtained from the PROMOVI study. Six untreated DMD samples were tested and the three with the lowest % dystrophin values were used as a pooled sample of the Negative Control. They were not from the week 48 but from the patients randomized to the week 24, 72, or 96 groups.

A copy of the Biopsy Specimen Collection and Examination Form was reviewed for each of the normal, DMD, and study 301 biopsy samples. The pathological examination was performed by (b) (4). It was noted that all samples were considered acceptable based on physical examination, measurement, absence of evidence of crushing by forceps, absence of freezing artifacts, fibrotic and/or adipose tissue content using H&E stained sections, and fiber orientation. No samples appear to be rejected based on the quality assessment in their tissue allocation SOP. A copy of the exon mutations and patient ages of each of the blinded samples was provided by the Sponsor, without reference to the sample identification.

*Sample designation and western blot procedure:* Each pair of blinded, individual patient samples were randomized and randomly labeled as either ‘Ford’ or ‘Chevy’ (b) (4). The samples were shipped from (b) (4) and stored at -20°C at Corvallis, OR. (b) (4)

Quantitation of images and data analyses: Each of the films was analyzed for dystrophin band density with ImageQuant (version 8.1) software (b) (4). A PowerPoint presentation with each of the steps involved and as observed on June 21-24 was provided by the Sponsor.

(b) (4)

The Microsoft Excel table print-outs provided by the Sponsor showed the interim analysis with raw numbers of % dystrophin the R-square value whether the R-square value was a pass or fail

(b) (4)



At the end of the inspection, two CD-ROMs were provided by Mr. Voss with all raw and analyzed data files. The inspection was closed with a scientific discussion with (b) (4) (b) (4) John Voss, M.S., and (b) (4) about (1) need for improvement of the current western blotting with a more robust detection and quantitation method that allows consistent quantitation at low levels of dystrophin, (2) the need for more robust assays, such as quantitative mass spectrometry, with greater precision and (3) the need for a more reliable reference standard, such as recombinant protein or cell line-based extracts, with lower inherent variability to allow precise quantitation of relative % normal dystrophin. The Sponsor acknowledged the feedback and stated that they are in the process of further developing their protein analyses methods and will be submitting a proposal for using a skeletal muscle myoblast cell line-based reference standard in the near future.

***Reviewer's comments:** The western blotting procedure for the biopsy samples appeared to have been conducted within the scope of the sponsor's predetermined standard operating procedures. I and the other FDA inspectors followed the western blotting procedure from the removal of samples from the freezer to the densitometric quantitation and did not observe any inappropriate manipulation. At no point did we have reason to believe that the sample blinding was compromised. The technicians were observed to be diligent and competent in the performance of the bioassay. The Sponsor could improve upon the consistency of the detection portion of the method and was advised to consider other more robust detection systems and reference standards in the future. Each of the additional analyses conducted in our presence, such as the overlaid chromatogram traces, appeared to be obtained with a sound scientific justification of its usefulness to clarify the relative dystrophin levels between the samples as observed with the protocol.*

**2. Review of dystrophin bioassay information from study 4658-301 in Sarepta’s NDA amendment 42 and study report SR-CR-16-003 submitted on 6/27/2016:**

Based on a review of the study report SR-CR-16-003, I was able to match each of the data points that passed acceptance criteria and used for their data table on page 17 (**Appendix 5**).

Powerpoint slides were provided to the Division of Neurology Products (Dr. Ron Farkas) on 6/28/2016 showing a line-by-line comparison of each of the data points with QC-checked summary tables we were provided during the on-site inspection.

The following data points from the failed gels didn’t match the summary data table I had from the inspection but did match the original worksheet from the technicians. Neither of these data points was used in the analyses by the sponsor because these are from failed gels so they should not impact any of the mean values.

1. Patient ID 301-07, Gel 13, we were given 0 and 0 as the numbers for lane 7 and 8. The sponsor has reported 0.04 and 0.22. The original data worksheet confirms 0.04 and 0.22. This gel failed its R-square acceptance criteria so this data point is not included in the sponsor’s analysis.
2. Patient ID 301-12, Gel 24, we were given 0.02 as the value for Lane 7. The sponsor has reported 0.01. The original data worksheet confirms 0.01. This gel failed its R-square acceptance criteria so this data point is not included in the sponsor’s analysis.

*Reviewer’s comments: The raw % dystrophin data that passed predefined acceptance criteria and submitted by the Sponsor was in agreement with the raw data obtained on site at the Corvallis, OR, testing laboratory. The two exceptions noted above for the data that failed quality control assessments were in agreement with the original data worksheets and not used for calculation of the % dystrophin values and hence should not impact the overall findings.*

*The Division of Neurology Products (ODEI/OND) will be conducting a review of the clinical efficacy and interpretation of the clinical implications of the % dystrophin findings.*

## Appendix 1

Western blot analysis schedule and sample loading sequence of the gels (provided by Sarepta)

### WESTERN BLOT ANALYSIS SCHEDULE

DAY 1-2: JUNE 20 & 21 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
1	1a	HMW	4%	2%	1%	0.5%	0.25%	Ford-22559 (1.5X)	Chevy-22559 (1.5X)	Neg Ctrl	HMW
2	1b	HMW	4%	2%	1%	0.5%	0.25%	Ford-22559 (1.5X)	Chevy-22559 (1.5X)	Neg Ctrl	HMW
3	2a	HMW	4%	2%	1%	0.5%	0.25%	Ford-27336 (2X)	Chevy-27336 (2X)	Neg Ctrl	HMW
4	2b	HMW	4%	2%	1%	0.5%	0.25%	Ford-27336 (2X)	Chevy-27336 (2X)	Neg Ctrl	HMW
5	3a	HMW	4%	2%	1%	0.5%	0.25%	Ford-24422 (1X)	Chevy-24422 (2X)	Neg Ctrl	HMW
6	3b	HMW	4%	2%	1%	0.5%	0.25%	Ford-24422 (1X)	Chevy-24422 (2X)	Neg Ctrl	HMW
7	4a	HMW	4%	2%	1%	0.5%	0.25%	Ford-27138 (1X)	Chevy-27138 (1X)	Neg Ctrl	HMW
8	4b	HMW	4%	2%	1%	0.5%	0.25%	Ford-27138 (1X)	Chevy-27138 (1X)	Neg Ctrl	HMW
9	5a	HMW	4%	2%	1%	0.5%	0.25%	Ford-28500 (2.5X)	Chevy-28500 (1X)	Neg Ctrl	HMW
10	5b	HMW	4%	2%	1%	0.5%	0.25%	Ford-28500 (2.5X)	Chevy-28500 (1X)	Neg Ctrl	HMW
11	6a	HMW	4%	2%	1%	0.5%	0.25%	Ford-24986 (1X)	Chevy-24986 (2X)	Neg Ctrl	HMW
12	6b	HMW	4%	2%	1%	0.5%	0.25%	Ford-24986 (1X)	Chevy-24986 (2X)	Neg Ctrl	HMW

DAY 3-4: JUNE 22 & 23 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
13	1a	HMW	4%	2%	1%	0.5%	0.25%	Ford-20841 (1X)	Chevy-20841 (2X)	Neg Ctrl	HMW
14	1b	HMW	4%	2%	1%	0.5%	0.25%	Ford-20841 (1X)	Chevy-20841 (2X)	Neg Ctrl	HMW
15	2a	HMW	4%	2%	1%	0.5%	0.25%	Ford-22355 (1.5X)	Chevy-22355 (1.5X)	Neg Ctrl	HMW
16	2b	HMW	4%	2%	1%	0.5%	0.25%	Ford-22355 (1.5X)	Chevy-22355 (1.5X)	Neg Ctrl	HMW
17	3a	HMW	4%	2%	1%	0.5%	0.25%	Ford-28907 (2X)	Chevy-28907 (1X)	Neg Ctrl	HMW
18	3b	HMW	4%	2%	1%	0.5%	0.25%	Ford-28907 (2X)	Chevy-28907 (1X)	Neg Ctrl	HMW
19	4a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29648 (2X)	Chevy-29648 (2X)	Neg Ctrl	HMW
20	4b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29648 (2X)	Chevy-29648 (2X)	Neg Ctrl	HMW
21	5a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29727 (1X)	Chevy-29727 (1X)	Neg Ctrl	HMW
22	5b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29727 (1X)	Chevy-29727 (1X)	Neg Ctrl	HMW
23	6a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29751 (1X)	Chevy-29751 (1X)	Neg Ctrl	HMW
24	6b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29751 (1X)	Chevy-29751 (1X)	Neg Ctrl	HMW

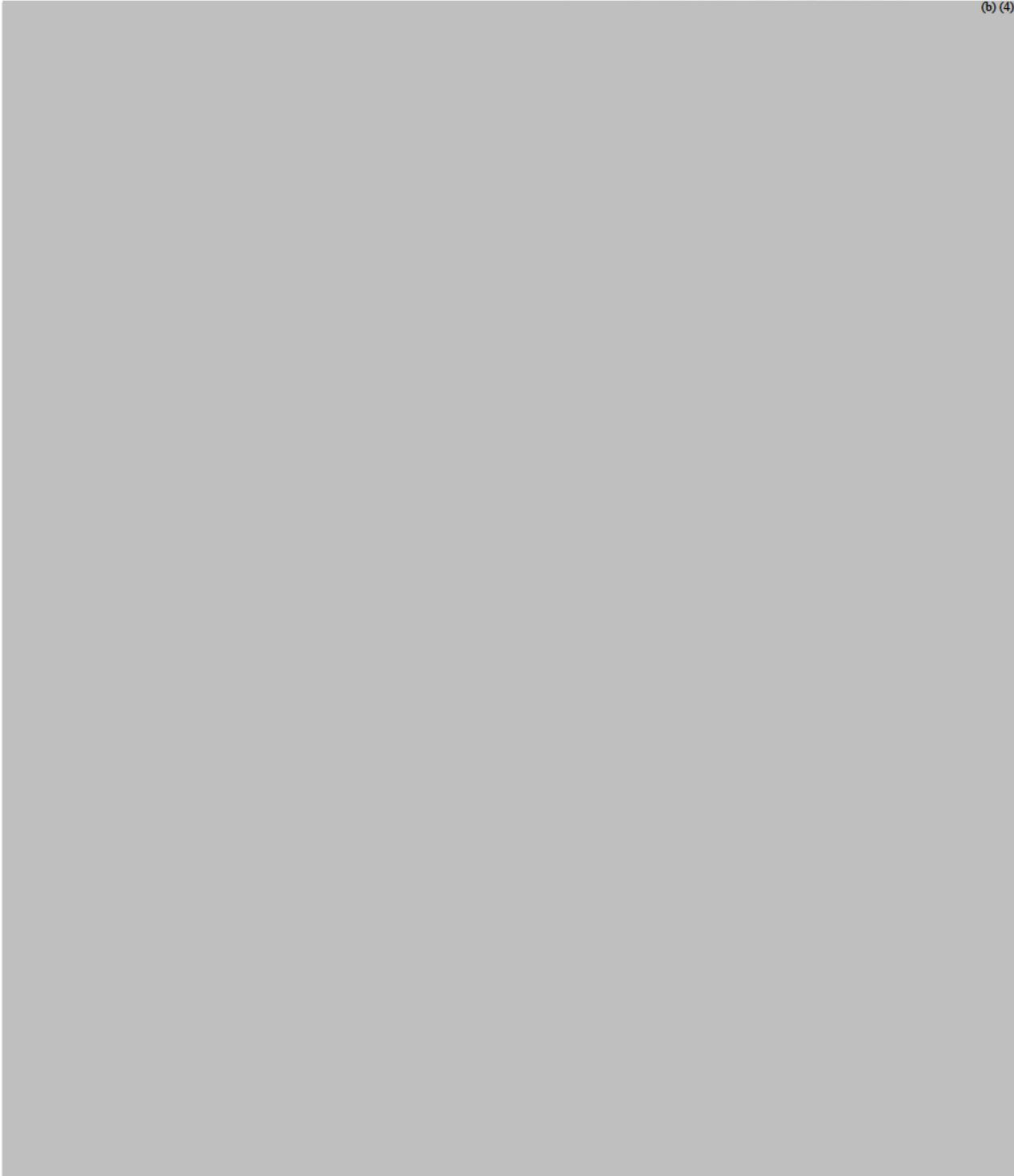
### WESTERN BLOT ANALYSIS SCHEDULE

DAY 3-4: JUNE 22 & 23 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
25	7a	HMW	4%	2%	1%	0.5%	0.25%	Ford-25715 (1X)	Chevy-25715 (2X)	Neg Ctrl	HMW
26	7b	HMW	4%	2%	1%	0.5%	0.25%	Ford-25715 (1X)	Chevy-25715 (2X)	Neg Ctrl	HMW

**Appendix 2**

*Raw dystrophin antibody-probed membranes for each of the western blot samples (Images provided by Sarepta)*



### Appendix 3

Three examples of chromatographic traces of the dystrophin quantitation from Lanes 7 and 8 using ImageQuant software (provided by Sarepta)

Image Filename: SR-CR-16-003\_Gel#5\_DYS1\_30min.tif

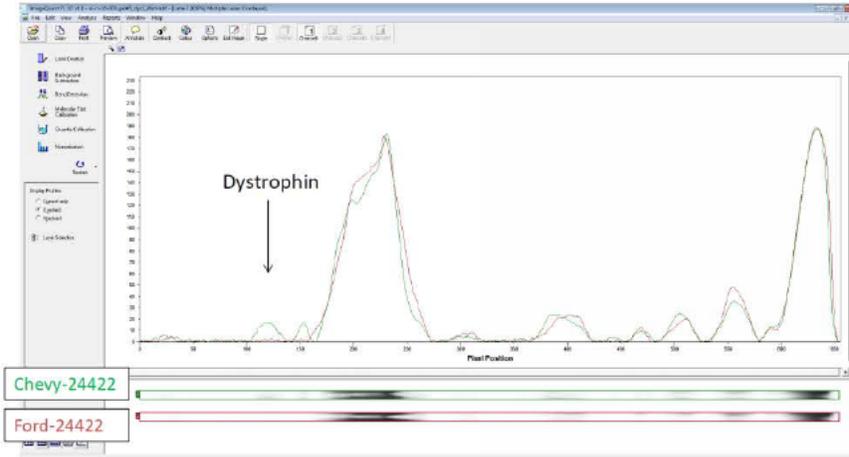


Image Filename: SR-CR-16-003\_Gel#9\_DYS1\_30min.tif

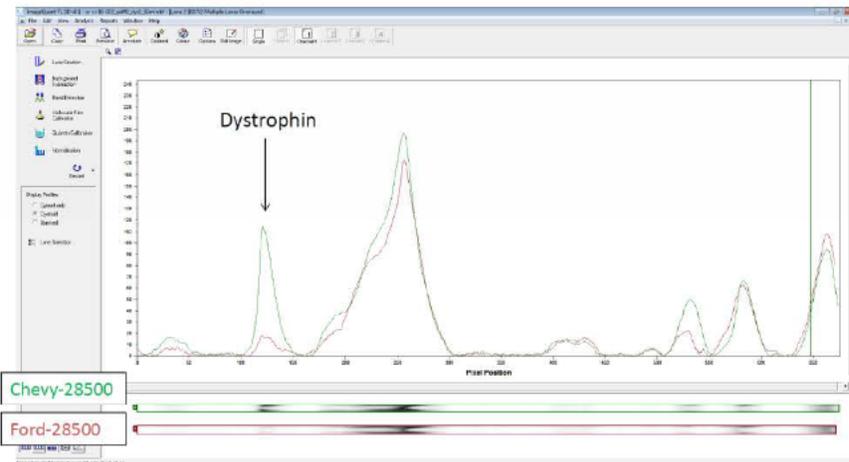
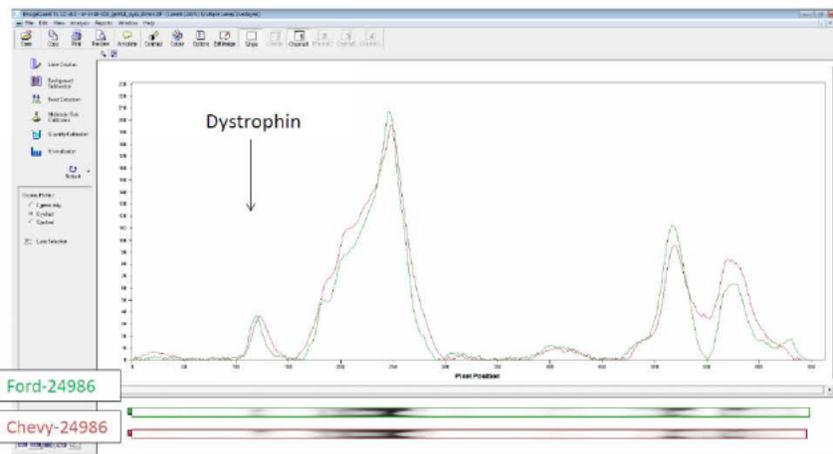


Image Filename: SR-CR-16-003\_Gel#11\_DYS1\_30min.tif



#### Appendix 4

Summary raw data tables showing all individual data points and whether they passed or failed acceptance criteria from the 15, 20, or 30 minute film exposures (Three tables below provided by Sarepta)

SR-CR-16-003: DYS1 - 15 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
13	1a	0.00	0.00	0.38	Fail	67389 (47602)	Pass
14	1b	0.17	0.42	0.97	Pass	64418 (58077)	Pass
15	2a	0.08	0.08	0.95	Pass	37476 (58536)	Fail
16	2b	0.14	0.05	0.83	Fail	21696 (20615)	Pass
17	3a	1.17	0.14	0.98	Pass	22073 (35280)	Fail
18	3b	1.57	0.24	0.98	Pass	49106 (37627)	Pass
19	4a	0.11	0.12	0.93	Pass	40030 (8873)	Pass
20	4b	0.05	0.11	0.98	Pass	35884 (39241)	Fail
21	5a	0.31	0.01	0.98	Pass	110706 (48990)	Pass
22	5b	0.63	0.08	0.93	Pass	93278 (52055)	Pass
23	6a	0.09	0.02	0.91	Pass	77556 (51352)	Pass
24	6b	0.02	0.00	0.78	Fail	108111 (64389)	Pass
25	8a	0.34	0.34	0.96	Pass	38943 (83782)	Fail
26	8b	0.18	0.21	0.97	Pass	20460 (19812)	Pass

SR-CR-16-003: DYS1 - 20 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
1	1a	0.14	0.27	0.99	Pass	14425 (8649)	Pass
2	1b	0.07	0.21	0.96	Pass	39798 (15235)	Pass
3	2a	0.36	0.35	0.99	Pass	26926 (14147)	Pass
4	2b	0.10	0.12	0.90	Pass	47296 (73361)	Fail
5	3a	0.13	0.50	0.98	Pass	22397 (31305)	Fail
6	3b	0.09	0.22	1.00	Pass	64945 (29089)	Pass
7	4a	0.04	0.08	0.95	Pass	44795 (16235)	Pass
8	4b	0.04	0.13	0.89	Fail	60880 (35534)	Pass
9	5a	0.10	1.08	0.80	Fail	86479 (40898)	Pass
10	5b	0.07	0.74	1.00	Pass	33696 (13462)	Pass
11	6a	0.30	0.37	0.97	Pass	31429 (30177)	Pass
12	6b	0.15	0.18	0.94	Pass	23477 (32971)	Fail
13	1a	0.01	0.01	0.11	Fail	87486 (71878)	Pass
14	1b	0.02	0.23	0.96	Pass	114817 (88315)	Pass
15	2a	0.04	0.05	0.90	Pass	82129 (91951)	Pass
16	2b	0.34	0.06	0.72	Fail	41439 (28302)	Pass
17	3a	0.91	0.08	0.99	Pass	78991 (47683)	Pass
18	3b	2.01	0.47	0.79	Fail	72064 (110397)	Fail
19	4a	0.01	0.22	0.91	Pass	78641 (33905)	Pass
20	4b	0.01	0.03	0.93	Pass	79184 (88118)	Fail
21	5a	0.09	0.00	0.75	Fail	187873 (38528)	Pass
22	5b	0.54	0.02	0.94	Pass	127964 (74633)	Pass
23	6a	0.00	0.00	0.80	Fail	131413 (58017)	Pass
24	6b	0.00	0.00	0.10	Fail	133242 (88876)	Pass
25	8a	0.20	0.32	0.65	Fail	33377 (88614)	Fail
26	8b	0.08	0.08	0.91	Pass	39914 (30132)	Pass

SR-CR-16-003: DYS1 - 30 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
1	1a	0.15	0.22	0.98	Pass	28142 (11562)	Pass
2	1b	0.11	0.29	0.99	Pass	43028 (10859)	Pass
3	2a	0.49	0.50	0.96	Pass	25657 (32471)	Fail
4	2b	0.12	0.26	0.92	Pass	49843 (76849)	Fail
5	3a	0.06	0.50	0.99	Pass	25008 (24738)	Pass
6	3b	0.06	0.24	0.99	Pass	64307 (34135)	Pass
7	4a	0.04	0.10	0.96	Pass	41141 (20779)	Pass
8	4b	0.06	0.19	0.83	Fail	51902 (41555)	Pass
9	5a	0.10	0.92	0.87	Fail	97732 (52789)	Pass
10	5b	0.17	1.02	0.98	Pass	60795 (11082)	Pass
11	6a	0.42	0.48	0.96	Pass	32341 (37122)	Fail
12	6b	0.29	0.46	0.96	Pass	29677 (34028)	Fail
13	1a	0.21	0.33	0.74	Fail	57768 (65008)	Fail
14	1b	0.04	0.77	0.70	Fail	102231 (81450)	Pass
15	2a	0.03	0.03	0.91	Pass	76752 (110138)	Fail
16	2b	0.34	0.04	0.71	Fail	46083 (40425)	Pass
17	3a	1.11	0.08	0.96	Pass	60216 (61057)	Fail
18	3b	3.91	0.48	0.99	Pass	81999 (89679)	Fail
19	4a	0.09	0.15	0.93	Pass	58708 (28376)	Pass
20	4b	0.00	0.05	0.95	Pass	66033 (80195)	Fail
21	5a	0.11	0.00	0.28	Fail	175676 (80890)	Pass
22	5b	0.49	0.03	0.92	Pass	110870 (50983)	Pass
23	6a	0.02	0.00	0.86	Fail	95415 (92390)	Pass
24	6b	0.00	0.00	0.19	Fail	127200 (95678)	Pass
25	8a	0.10	0.11	0.28	Fail	48731 (108832)	Fail
26	8b	0.04	0.08	0.90	Pass	42916 (29626)	Pass

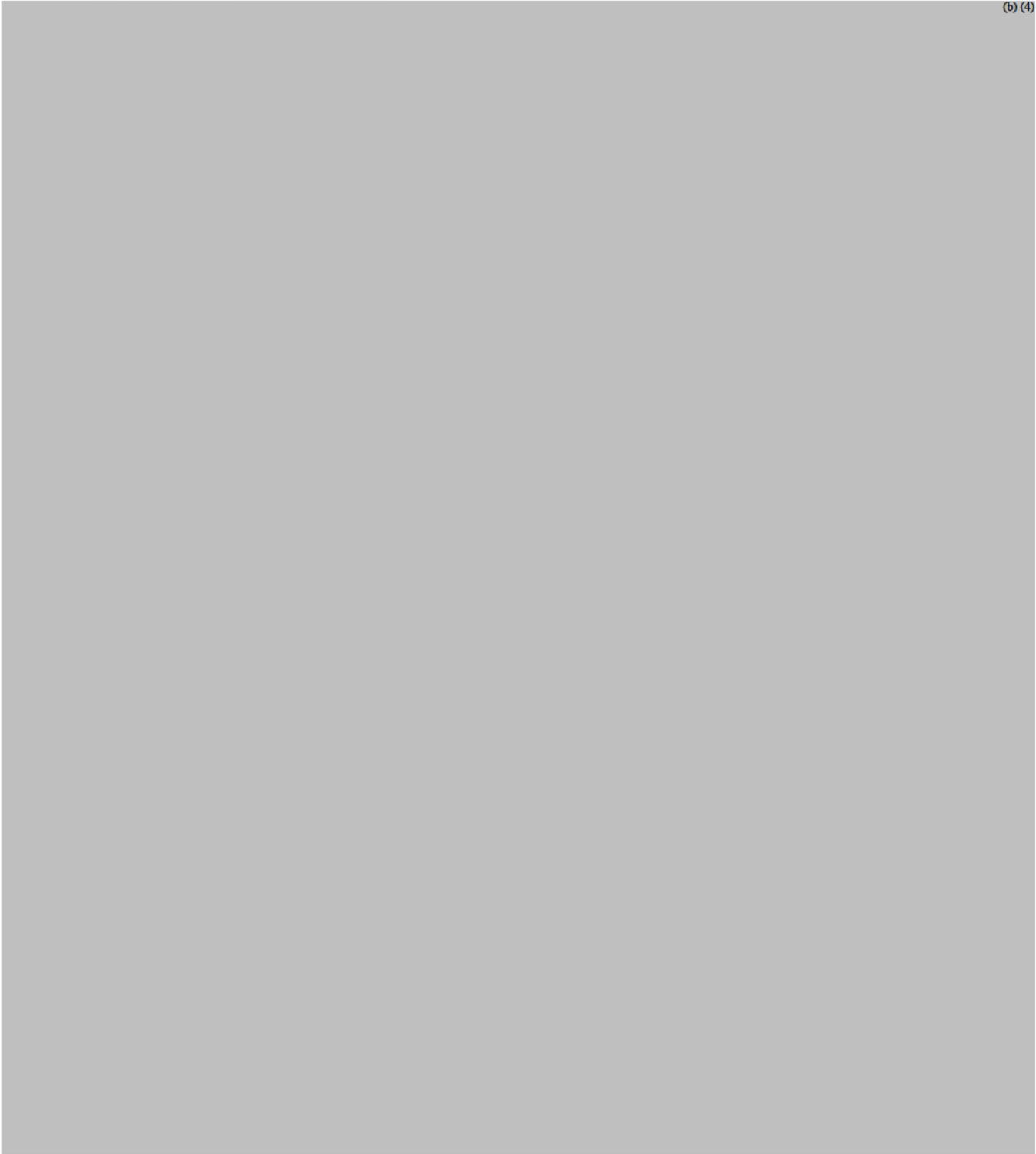
**Appendix 5**

*Data listing from report 4658-301-SR-CR-16 of Dystrophin Western blot results with all raw values (provided by Sarepta)*

SR-CR-16-003 Patient WB Analysis  
4658-301 Week 48 Interim Analysis

June 27, 2016

(b) (4)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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V ASHUTOSH RAO  
07/15/2016

AMY S ROSENBERG  
07/15/2016

STEVEN KOZLOWSKI  
07/15/2016

**Recommendation: Approve with Post-marketing Commitments**

**NDA 206488**

**Review 1  
May 6, 2016**

<b>Drug Name/Dosage Form</b>	Exondys 51 (eteplirsen injection)
<b>Strength</b>	50 mg/mL
<b>Route of Administration</b>	Intravenous infusion
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Sarepta Therapeutics
<b>US agent, if applicable</b>	N/A

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Mari Chelliah	Branch 1/DNDP 1/ONDP
Process	Sung Kim	Branch VII/DPA3/OPF
Microbiology	Denise Miller	OPQ/OPF/DMA/Branch II
Facility	Zhong Li	OPQ/OPF/DIA/IABI
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	Jim Laurenson	OPQ/ONDP/EA Team

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>	<b>DISCIPLINE(S) AFFECTED</b>
Amendment	9/1/2015	Quality Response to IR
Amendment	9/16/2015	Quality Response to IR
Amendment	10/1/2015	Quality Response to IR
Amendment	10/5/2015	Quality Response to IR
Amendment	10/13/2015	Quality Response to IR
Amendment	10/20/2015	Quality Response to IR
Amendment	10/30/2015	Quality Response to IR
Amendment	12/17/2015	Quality Response to IR

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## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	N/A	Adequate information in NDA
	Type III		N/A	N/A	Adequate information in NDA	
	Type V		Adequate	26-Jan-2016	Review by D. Miller	
	Type V		Adequate	25-Aug-2015	Review by L. Shelton	
	Type V		Adequate	06-Jul-2016	Review by J. Swoboda	

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77429	Eteplirsen for DMD

**2. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Complete	Assignment of 18 month shelf for eteplirsen injection based on available stability data.	05-Jan-2016	Dr. Zhuang Miao
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

NDA 206488

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing and controls (CMC) perspective, NDA 206488 is recommended for approval with the post-marketing commitments (PMCs) described in Section I.B below.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has agreed to the following post-marketing commitments:

1. Investigate the root cause of the increasing assay trend observed in the drug product stability study.
2. Revalidate the accuracy of the in-process (b) (4) method used during drug product manufacture.
3. Revalidate the robustness of the in-process (b) (4) method in terms of (b) (4).
4. Investigate the consistent bias in the in-process (b) (4) and the release (b) (4) assay results.

The recommended time frame for fulfillment of the post-marketing commitments is no later than one year following NDA approval. If the Agency does not approve the application during the current review cycle, it is probable that the applicant will complete the studies prior to resubmission of the application.

### II. Summary of Quality Assessments

The applicant proposes use of eteplirsen, a synthetic oligonucleotide to treat Duchenne muscular dystrophy (DMD). DMD, a rare recessive X-linked form of muscular dystrophy, results in progressive muscle weakness and loss of muscle mass, loss of movement, and ultimately death. The disease is caused by mutations in *DMD*, the gene encoding dystrophin, a sarcolemma protein critical to the structural stability of myofibers in skeletal and cardiac muscle. Dystrophin mutations induce a shift in the open reading frame of the dystrophin transcript, leading to the absence of functional dystrophin protein. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Thus, eteplirsen is intended to restore the open reading frame for patients with *DMD* mutations amenable to exon 51 skipping and induce production of an internally deleted, functional dystrophin protein.

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**A. Drug Substance Quality Summary for Eteplirsen**

The drug substance, eteplirsen, contains a sequence of 30 linked (dimethylamino)-phosphorodiamidate morpholino subunits. It is functionalized with a hydrophilic triethylene glycol-derived “tail” at the 5' end that enhances aqueous solubility. The chemical name (CAS Index Name) for eteplirsen is:

RNA, [P-deoxy-P-(dimethylamino)] (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a→ 5') (C-m5U-C-C-A-A-C-A-m5U-C-A-A-G-G-A-A-G-A-m5U-G-G-C-A-m5U-m5U-m5U-C-m5U-A-G), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-N,N- dimethylaminophosphonamidate]

\* Note that “m5U”, which stands for 5-methyluracil, is the abbreviation for thymine base when thymine is named as part of RNA.

Each subunit of eteplirsen is attached to one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, and thymine). Eteplirsen differs from natural ribose-based oligonucleotides, and synthetic phosphorothioate oligonucleotides, in that: a) the heterocyclic bases of eteplirsen are attached to a morpholino group, not a ribose unit, and b) the linkages between subunits are neutral, not negatively charged. (b) (4)

(b) (4)

(b) (4)

The applicant has adequately characterized the drug substance using proton ( $^1\text{H}$ ), carbon ( $^{13}\text{C}$ ), and phosphorus ( $^{31}\text{P}$ ) nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), sequence determination by acid hydrolysis with LC/MS, and X-ray diffraction.

The drug substance is manufactured (b) (4)

(b) (4)

(b) (4)

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(b) (4)

The applicant has developed adequate controls for the (b) (4) starting materials. Critical parameters (b) (4) designated (b) (4) (b) (4) are adequately defined and controlled.

The release specification for eteplirsen includes tests for drug substance CQAs such as appearance, identity (MS and proof of structure by sequencing), assay, purity, specified impurities, residual solvents, residue on ignition, water content, pH, bioburden, and bacterial endotoxins. The applicant has provided adequate characterization of impurities and justification for the proposed acceptance criteria. Non-compendial analytical methods are validated for critical analytical parameters such as linearity, specificity, precision, accuracy, solution stability, and robustness, and are suitable for their intended use.

Based on acceptable stability data from primary and supportive stability batches, a retest period of (b) (4) months (b) (4) is established for the drug substance when stored in a (b) (4) bottle (b) (4).

## B. Drug Product Quality Summary for Eteplirsen Injection

Eteplirsen injection is a sterile solution containing 50 mg eteplirsen per mL in a pH 7.5 aqueous phosphate buffer. The solution is made isotonic with (b) (4) (b) (4). The applicant proposes two single dose vial configurations, 100 mg/2 mL and 500 mg/10 mL. The product does not contain an antimicrobial preservative. All excipients are within the ranges used in previously approved intravenous drug products.

The proposed dose of eteplirsen is 30 mg/kg administered by iv infusion once per week. The product must be diluted in saline prior to use.

The commercial formulation differs from the formulation used in the Phase 2 study in that the (b) (4) (b) (4) (b) (4) the change (b) (4) is not considered clinically relevant.

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The commercial manufacturing process for eteplirsen injection consists of

(b) (4)

(b) (4)

(b) (4). In the NDA submission, the applicant proposed an assay acceptance criterion of 90.0% – 115.0%. The review team initially requested that the specification be revised to 90.0% – 110.0% and the applicant agreed. After further evaluation, the review team recommended that the applicant retain the original 90.0% – 115.0% range. The recommendation was based on the following considerations:

- DMD is a debilitating, and ultimately fatal, disease for which there are no approved drugs. Current standard of care includes use of glucocorticoids in conjunction with other palliative interventions. However, glucocorticoids do not halt disease progression and are associated with other undesirable effects.
- Based on discussions with the clinical division, there are no safety concerns associated with the 115.0% upper specification limit.
- During early clinical development, the product specification was 90.0% – 115.0%. Assay results for most batches of the earlier clinical formulations were at or above 100% of target.
- The applicant and the current contract manufacturer, (b) (4) have limited manufacturing experience. As the applicant gains additional manufacturing experience, it is expected that the assay values will likely become closer to the target value. In the interim, the 90.0% – 115.0% acceptance criterion is expected to minimize the risk of discarding a batch that would otherwise be acceptable from an efficacy and safety perspective.

To further mitigate risks due to product quality, the review team has requested that the applicant provide post-marketing commitments (PMC) to revalidate the in-process (b) (4) (b) (4) and investigate to root cause(s) for the discrepancy between (b) (4) results. The applicant has agreed to the requested PMCs, and to reevaluate the product specification as they gain more manufacturing experience.

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The release specification for eteplirsen injection includes tests for drug product CQAs such as appearance, identity (molecular weight), assay, purity, specified impurities, elemental impurities, pH, osmolality, sterility, bacterial endotoxins, and particulate matter. All observed impurities are derived from the drug substance; there are no formulation specific degradation products. Non-compendial analytical procedures used for product release are similar to those used for the drug substance. The primary differences are related to sample preparation. The analytical procedures are adequately validated and suitable for their intended use.

Based on evaluation of stability data from primary and supportive batches, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°C).

**C. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	EXONDYS 51
<b>Non Proprietary Name of the Drug Product</b>	Eteplirsen Injection
<b>Non Proprietary Name of the Drug Substance</b>	Eteplirsen
<b>Proposed Indication(s) including Intended Patient Population</b>	Treatment of Duchenne muscular dystrophy in the subset of patients with mutations near exon 51 of the <i>DMD</i> gene that are amenable to exon 51 skipping.
<b>Duration of Treatment</b>	Chronic
<b>Maximum Dose</b>	30 mg per kg of body weight once weekly
<b>Alternative Methods of Administration</b>	None

**D. Biopharmaceutics Considerations**

Not applicable.

**E. Novel Approaches**

The applicant did not employ any novel approaches in the development or manufacture of eteplirsen injection.

**F. Any Special Product Quality Labeling Recommendations**

Eteplirsen injection should be refrigerated (5°C). The product must be diluted with saline prior to infusion. The product does not contain an antimicrobial preservative and should be used within 4 hours after dilution if stored at room temperature, or 24 after dilution if refrigerated. Any unused portion should be discarded.

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**G. Life Cycle Knowledge Information (see Attachment A)****H. Assessment of Environmental Analysis**

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed, along with additional literature given eteplirsen is a new molecular entity and within a relatively new class of drugs (synthetic oligonucleotides). The claim was found to be acceptable.

**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY****Application Technical Lead Signature:**

The OPQ review team recommends approval of NDA 206488.

**Martha R. Heimann -S**

Digitally signed by Martha R. Heimann -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, 0.9.2342.19200300.100.1.1=1300091527,  
cn=Martha R. Heimann -S  
Date: 2016.05.06 16:30:12 -04'00'

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**ASSESSMENT OF THE BIOPHARMACEUTICS****This section is not applicable.**

APPEARS THIS WAY ON ORIGINAL

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## ASSESSMENT OF MICROBIOLOGY

32. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

## Applicant's Response:

**Reviewer's Assessment:****1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)  
MODULE 3.2: BODY OF DATA****S DRUG SUBSTANCE – NA**

**Review note:** The drug substance is a synthetic lyophilized product that is not sterile. It is tested for Total Aerobic Microbial Count (specification NMT (b) (4)) and for bacterial endotoxin (specification NMT (b) (4)).

**P DRUG PRODUCT****P.1 Description of the Composition of the Drug Product**

- Description of drug product – clear, colorless sterile aqueous solution at 50 mg/mL provided in two volumes, 2.0 mL or 10 mL vials. The product is single use and not preserved. The pH of the solution is 7.5 and is to be diluted prior to administration. The diluent is normal saline that is not provided.
- Drug product composition – Composition was provided in Table 1 of application section 3.2.P.1.
- Description of container closure system –
  - Vials: Type I (b) (4) vials
    - 10 mL vial with 20 mm opening
    - 2 mL vial with 13 mm opening
  - Stoppers
    - Stopper (b) (4)
    - Stopper (b) (4)

**P.2 Pharmaceutical Development****P.2.5 Microbiological Attributes**

- Container-Closure Integrity (CCI) – CCI was tested on both the 2 mL vial and the 10 mL vial using microbial and dye ingress methods.
- Microbial Ingress: Studies were performed on both the 2 mL vial and the 10 mL vial presentations. (b) (4)  
(b) (4)

The result was no growth after 7 days incubation. Challenge conditions and positive control information was not provided; this information was

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requested in the IR dated 09 September 2015.

- Dye Ingress: Two studies were performed.

(b) (4)

(b) (4)

Dye penetration was not observed. The summary did not provide information on the level of detection for the dye ingress test or whether there were positive controls included. This was requested in a 09 September 2015 follow up communication to the 74 day letter.

**Information Request dated 09 September 2015, Question 6:**

1) *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?*

**Response dated 16 September 2015:** The summary of the testing for the dye ingress and microbial ingress testing as present in 3.2.P.2.5 was reviewed to include the requested information. The revised document is provided along with this response, refer to Table 1. (Reviewer note, Table 1 listed section 3.2.P.2.5 was updated for this response).

**Review of Response:**

Microbial Ingress: The testing was performed on vials filled with TSB media. There were 2 positive controls used

(b) (4)

(b) (4)

Dye Ingress: There were two dye ingress studies performed, both were visual detection.

(b) (4)

(b) (4)

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(b) (4). The vials were visually examined for dye ingress. The challenged vials were negative for dye ingress and the positive controls were positive.

The CCI testing is adequate and supports the ability of the container closure system to exclude microbial contamination. The ability of the container closure system to exclude microbial contamination over the shelf life is addressed in the stability program.

- Preservative Effectiveness - NA
- Justification for not having a microbial limit specification for a non-sterile drug product - NA

**ADEQUATE**

**REVIEWER COMMENT** – The information provided is adequate, the integrity of the Container Closure over the shelf life of the product is assessed in the stability program.

**P.3 Manufacture****P.3.1 Manufacturers**

The manufacturers were provided in Table 1 of section 3.2.P.3.1. The drug product is filled (b) (4). Release testing of the completed drug product is performed (b) (4).

**P.3.3 Description of the Manufacturing Process and Process Controls**

(b) (4)

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(b) (4)

**ADEQUATE**

**REVIEWER COMMENT** – The information provided for the facility and the process was acceptable.

**P.3.5 Process Validation and/or Evaluation**

(b) (4)

**ADEQUATE**

**REVIEWER COMMENT** – The (b) (4) validation demonstrated the ability (b) (4) (b) (4) to retain microorganisms under the proposed processing conditions.

**P.5 Control of Drug Product****P.5.1 Specifications****P.5.2 Analytical Procedures**

- Endotoxin – Endotoxin is tested following USP <85> (b) (4)

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The specification is NMT (b) (4) EU/mL. The dose is 30 mg/kg once per week for both adults and pediatrics. Since the dose is weight based, the worst case volume to be administered would be to an adult. An average adult of 70 kg would require 2100 mgs (42 mls at 50 mg/mL). The maximum potential endotoxin exposure of this dose is (b) (4) EU (b) (4) EU/kg/hour) which is below the (b) (4) EU/kg/hour limit as set in USP <85>. The specification is acceptable. The method suitability was not included. This was requested in a 09 September 2015 follow up communication to the 74 day letter.

**Information Request dated 09 September 2015, Question 5:**

- 5) *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.*

**Response dated 16 September 2015:** The method suitability testing was added to section 3.2.P.5.3 of the application.

**Review of Response:** The endotoxin testing is performed following UPS <85> (b) (4) (b) (4). Three batches were tested for enhancement/inhibition according to USP <85>. The product was tested at 4 dilutions within the maximum valid dilution; all demonstrated spike recoveries between (b) (4) % meeting the (b) (4) % acceptance criterion.

- Sterility – Sterility is tested following USP <71>, method and method suitability was not provided. The specification is no growth after 14 days. This was requested in a 09 September 2015 follow up communication to the 74 day letter.

**Information Request dated 09 September 2015, Question 4:**

- 4) *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.*

**Response dated 16 September 2015:** The method suitability testing was added to section 3.2.P.5.3 of the application.

**Review of Response:** The sterility testing is performed following USP <71> (b) (4) (b) (4). Method suitability was performed with both the 10 mL and 2 mL fill configurations using the USP indicator organisms. (b) (4)

- Microbial Limits - NA

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**ACCEPTABLE**

**REVIEWER COMMENT** – The information provided for the release testing of the subject drug product is acceptable.

**P.7 Container Closure System - NA****P.8 Stability****P.8.1 Stability Summary and Conclusion**

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY:  
STABILITY CONSIDERATIONS

Long term:  $5 \pm 3^{\circ}\text{C}$  for up to 36 months  
Sterility tested at 0, 12, 24, and 36 months  
Endotoxin tested at 0, and 36 months

Accelerated:  $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$  for 6 months  
No microbiological testing for this

**P.8.2 Post-Approval Stability Protocol and Stability Commitment**

The sponsor will complete the registration/long-term stability studies. The sponsor will also place one lot of drug product of each packaging configuration on stability annually if product is manufactured.

- Container Closure Integrity – Tested by sterility at 0, 12, 24, and 36 months on units under long term storage conditions.
- Endotoxin – Tested at 0, and 36 months on units under long term storage conditions.
- Microbial Limits - NA

**P.8.3 Stability Data**

Three lots of the 50 mg/mL 2 mL vial product were placed on stability, 83GD-DR01, 88GD-DR01, and 89GD-DR01. Data for up to 12 months was provided for one lot with data up to the 6 month time point provided to the other two lots.

Three lots of the 50 mg/mL 10 mL vial product were placed on stability, 84GD-DQ01, 85GD-DQ01, and 87GD-DQ01. Data for up to 12 months was provided for one lot with data up to the 6 month time point provided to the other two lots.

All data for the quality microbiological attributes met specification.

**ADEQUATE**

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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.

**2.3.P.7 Container/Closure System**

33. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Applicant's Response:**

**Reviewer's Assessment: see Question 32.**

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**A APPENDICES****A.2 Adventitious Agents Safety Evaluation**

34. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

**Applicant's Response:**

**Reviewer's Assessment: See Question 32.**

35. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:**

**Reviewer's Assessment: See Question 32.**

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY****Reviewer's Assessment and Signature:**

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

The recommendation is to approve.

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

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**Secondary Review Comments and Concurrence:**

I concur with the reviewer's assessment and recommendation of approval from the standpoint of Product Quality Microbiology.

**Neal J. Sweeney, Ph.D. 3/1/16**  
**Quality Assessment Lead (Acting)**  
**OPQ/OPF/DMA/Branch II**

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## ASSESSMENT OF ENVIRONMENTAL ANALYSIS

36. Is the applicant's claim for categorical exclusion acceptable?

37. Is the applicant's Environmental Assessment adequate for approval of the application?

**Applicant's Response:** The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). Specifically, the expected introduction concentration (EIC) of (b)(4) for eteplirsen, based on a maximum projected active usage of (b)(4) per year, was noted as lower than the 1 ppb categorical exclusion value. The required statement of no extraordinary circumstances, per 21 CFR 25.15(a), was included.

**Reviewer's Assessment:** The EIC of (b)(4) is approximately two orders of magnitude below the 1 ppb categorical exclusion value. The calculation appears accurate and reasonable. Therefore, the categorical exclusion claim is appropriate for the anticipated amount of drug to be used.

The required statement of no extraordinary circumstances was provided. No supporting information was provided (none is required), but given eteplirsen is a new molecular entity, and within a relatively new class of drugs, i.e., synthetic oligonucleotides (SOs), a detailed review of available data was conducted to determine the potential for significant environmental impact and thus the possibility of extraordinary circumstance such that an EA would be needed. Previous SO applications were reviewed and a literature search was conducted. The following findings indicated potential environmental risk:

1. CTD section 2.4, Nonclinical Overview, for the subject SO indicated that eteplirsen was metabolically stable in hepatic microsomes of all species tested, including humans. Excretion data only provided total radioactive label concentrations, however, which was not conclusive for whether eteplirsen was metabolized before excretion. Nevertheless, other data noted that SOs can be excreted whole (e.g., Vlassov et al., 1997; Rosie et al., 2007; EMA, 2013).
2. Some material safety data sheets (MSDSs), including for eteplirsen, state that SOs should not be released into the environment (GE Healthcare, 2015; Sarepta Therapeutics, 2014).
3. Some literature speculated that synthetic RNA could be reverse transcribed into complementary DNA to become incorporated into the cell's genome (Ho et al., 2000; Schmidt and de Lorenzo, 2012).

The following findings indicated low risk:

1. One MSDS stated that its SO product contains no substances known to be hazardous to

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the environment or that are not degradable in waste water treatment plants (GE Healthcare, 2015).

2. CTD section 2.4 also noted the following:
  - a. Eteplirsen was not genotoxic in the standard battery of assays, i.e., *in vitro* bacterial mutation, mammalian chromosome aberration, and *in vivo* mouse bone marrow micronucleus. Also, no pre-neoplastic or other proliferative lesions were observed in the 39-week toxicity study in monkey.
  - b. Toxicity of eteplirsen was evaluated in GLP-compliant repeat-dose studies in mdx (dystrophic) and nonmdx mice (12 weeks duration), juvenile Sprague-Dawley rats (10 weeks), and adult cynomolgus monkeys (12 and 39 weeks), resulting in no-observed-adverse-effect levels (NOAELs) at the highest dose level tested in mice (960 mg/kg/week, or 137 mg/kg/day) and monkeys (320 mg/kg/week, or 45 mg/kg/day). These doses likely would result in a predicted no effects concentration (PNEC) at (b) (4), which is substantially higher than the EIC of (b) (4).
3. NIH Guidelines (NIH, 2013) exempt synthetic nucleic acid molecules from special handling if they: (1) can neither replicate nor generate nucleic acids that can replicate in any living cell (e.g., oligonucleotides or other synthetic nucleic acids that do not contain an origin of replication or contain elements known to interact with either DNA or RNA polymerase), and (2) are not designed to integrate into DNA, and (3) do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight. The subject SO appears to meet these criteria.

Therefore, eteplirsen appears to be excreted whole, at least to some extent, and thus could be sufficiently stable to remain whole following wastewater treatment. The drug then could theoretically interact with aquatic organism and result in adverse effects through direct toxicity or perhaps even through mutations in germ cells. No data were found, however, to indicate that either such impacts could occur. Also, eteplirsen appears to have low toxicity and mutation potential, and is exempt from NIH handling guidelines. Therefore, this review concludes that no significant impact is expected from this action. A request for available environmental information from the applicant is recommended for purposes of researching this class of drugs more broadly.

**References:**

EMA, 2013, Assessment report, Kynamro Solution for injection 189mg.

GE Healthcare, 2015, Safety Data Sheet - RNA oligonucleotide,  
<http://dharmacon.gelifesciences.com/uploadedFiles/Resources/rna-oligo-sds-na.pdf>.

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Ho, M.W., Ryan, A., Cummins, J. and Traavik, T., 2000. Unregulated Hazards: 'Naked' and 'Free' Nucleic Acids. ISIS & TWN Report, London and Penang. [www.i-sis.org](http://www.i-sis.org).

National Institutes of Health (NIH), 2013, NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, [http://osp.od.nih.gov/sites/default/files/NIH\\_Guidelines.html](http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html).

Rosie ZY, Kim TW, Hong A, Watanabe TA, Gaus HJ, Geary RS. 2007. Cross-species pharmacokinetic comparison from mouse to man of a second-generation antisense oligonucleotide, ISIS 301012, targeting human apolipoprotein B-100. *Drug Metabolism and Disposition*. Mar 1;35(3):460-8.

Sarepta Therapeutics, 2014, Safety Data Sheet - Eteplirsen-AVI-4658, available through [www.msds.com](http://www.msds.com).

Schmidt, M. and de Lorenzo, V., 2012. Synthetic constructs in/for the environment: managing the interplay between natural and engineered Biology. *FEBS letters*, 586(15), pp.2199-2206.

Vlassov VV, Vlassova IE, Pautova LV. 1997. Oligonucleotides and polynucleotides as biologically active compounds. *Progress Nucleic Acid Research and Molecular Biology*. 1997; 57: 95-143

## OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

**Reviewer's Assessment and Signature:** The claim for a categorical exclusion from an EA is acceptable. A general correspondence is recommended that requests any readily available information on the environmental fate, toxicity, and risk of eteplirsen and similar SOs.

James P. Laurenson, April 7, 2016

**Secondary Review Comments and Concurrence:** I concur with this review and conclusion.

M. Scott Furness, April 11, 2016

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# I. Review of Common Technical Document-Quality (CTD-Q) Module 1 Labeling & Package Insert

## 1. Package Insert

### (a) “Highlights” Section (21CFR 201.57(a))

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use <sup>TM</sup> safely and effectively. See full prescribing information for .

EXONDYS 51 (eteplirsen) injection, for intravenous infusion.

Initial U.S. Approval: <<Insert four-digit year>>

[Redacted] (b) (4)

#### DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)

#### DOSAGE FORMS AND STRENGTHS

[Redacted] (b) (4)

#### CONTRAINDICATIONS

None (4)

[Redacted] (b) (4)

#### ADVERSE REACTIONS

[Redacted] (b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-844-727-3782 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

[Redacted] (b) (4)

Revised: <<insert month/year>>

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Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		Adequate
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths		

**Conclusion: Adequate**

**(b) "Full Prescribing Information" Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

**3 DOSAGE FORMS AND STRENGTHS**

(b) (4)

(b) (4) EXONDYS 51 is clear and colorless, and may have some opalescence.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

**Conclusion: Adequate**

NDA 206488

**#11: Description (21CFR 201.57(c)(12))****11 DESCRIPTION**

EXONDYS 51 (eteplirsen) is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single use (b)(4) vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 8.0 mg sodium chloride, USP; 0.2 mg potassium chloride, USP; 0.2 mg potassium phosphate monobasic, NF; 1.14 mg sodium phosphate dibasic, anhydrous, USP (b)(4) in water for injection, USP. The pH of the product may be adjusted with dilute hydrochloric acid or sodium hydroxide.

(b)(4)

(b)(4) Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in native DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The structure and base sequence of eteplirsen are depicted in Figure 1.

The molecular formula of eteplirsen is  $C_{364}H_{569}N_{177}O_{122}P_{30}$  and the molecular weight is 10305.7 daltons.



**NDA 206488**

If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		Adequate

**Conclusion: Adequate**

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**1.1. 16.1 How Supplied**

EXONDYS 51 is supplied in single use, (b) (4) vials (b) (4)  
 (b) (4)  
 (b) (4) NDC 60923-363-02  
 NDC 60923-284-10

**16.2 Storage**

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		Adequate
Storage conditions		Adequate

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Adequate

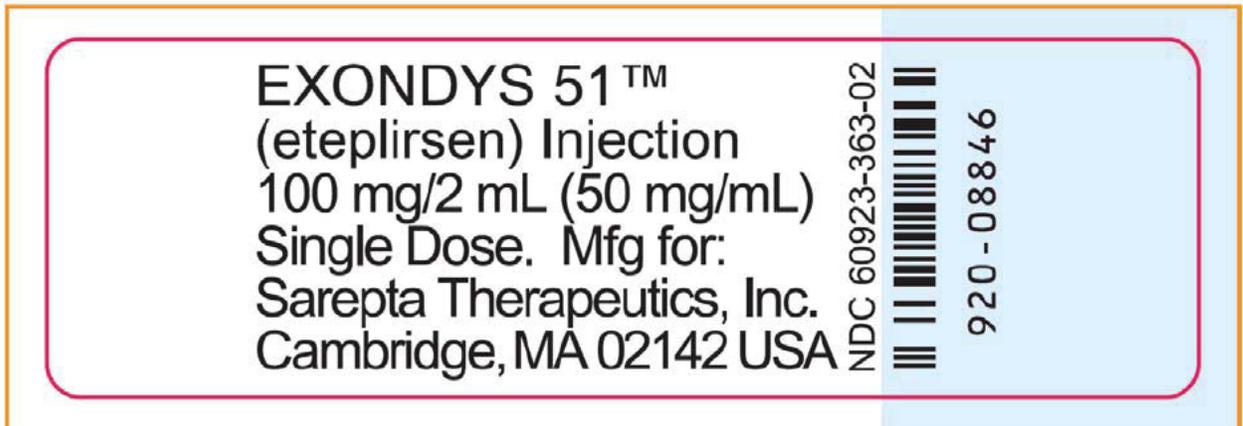
NDA 206488

**Conclusion: Adequate**

*Note that the sponsor refers to the drug product in the vials as 'single use' only. However, as per the FDA Draft Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry](#), these vial are strictly 'single dose' and the Agency is retiring the term "single-use". Based on the FDA's recommendation, the sponsor has revised this term on the container and carton labeling (see below). The packaged insert will be revised accordingly during the labeling review process.*

**2. Container and Carton Labeling**

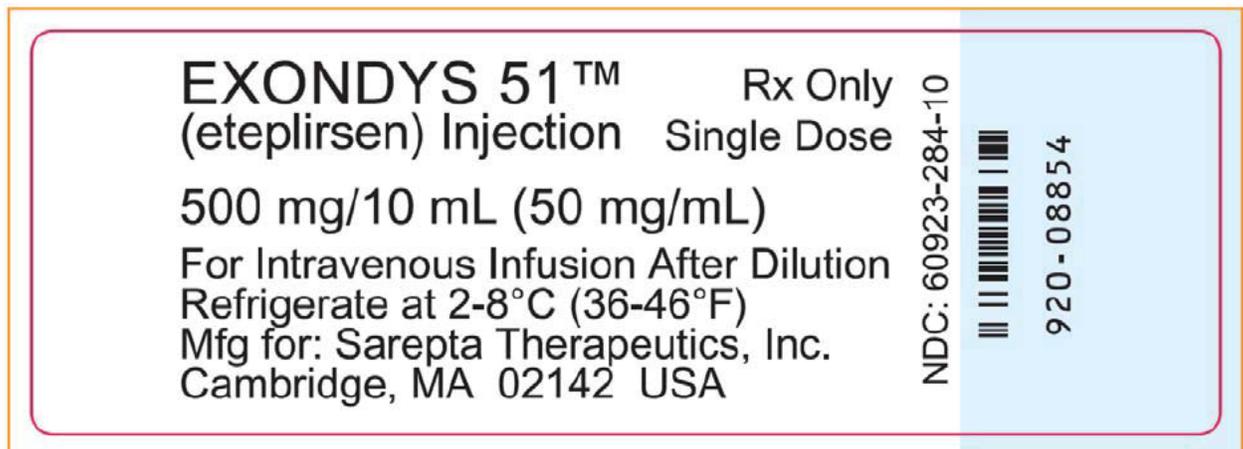
**1) Immediate Container Label**



EXONDYS 51™  
 (eteplirsen) Injection  
 100 mg/2 mL (50 mg/mL)  
 Single Dose. Mfg for:  
 Sarepta Therapeutics, Inc.  
 Cambridge, MA 02142 USA

NDC 60923-363-02

920-08846



EXONDYS 51™ Rx Only  
 (eteplirsen) Injection Single Dose  
 500 mg/10 mL (50 mg/mL)  
 For Intravenous Infusion After Dilution  
 Refrigerate at 2-8°C (36-46°F)  
 Mfg for: Sarepta Therapeutics, Inc.  
 Cambridge, MA 02142 USA

NDC: 60923-284-10

920-08854

**NDA 206488**

*Reviewer's Assessment:*

<b>Item</b>	<b>Comments on the Information Provided in NDA</b>	<b>Conclusions</b>
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))	Label for the 10.0 mL vial lists the route of administration, but the 2.0 mL vial does not. However, this is acceptable as per 21 CFR 201.10(i)(2) (too small a label to print all the details required by 21.CFR 201.100(b)(3))	Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Both the container labels do not list the inactive ingredients. However, this is acceptable as per 21 CFR 201.10(i)(2) (too small a label to print all the details required by 21.CFR 201.100(b)(3))	Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	The label for the 2 mL does not list Rx only statement. However, this is acceptable as per 21 CFR 201.10(i)(2) (too small a label to print all the details required by 21.CFR 201.100(b)(3))	Adequate
Storage (not required)	While the label for the 10 mL vials lists the storage conditions, the label for the 2 mL vials does not. Although this is not a deficient, we will recommend the sponsor to harmonize the two labels so that they appear similar.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The sponsor revised the middle number of the NDC on the recommendation of the DMEPA to minimize the confusion.	Adequate

**NDA 206488**

<b>Item</b>	<b>Comments on the Information Provided in NDA</b>	<b>Conclusions</b>
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		--

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

\*\*Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

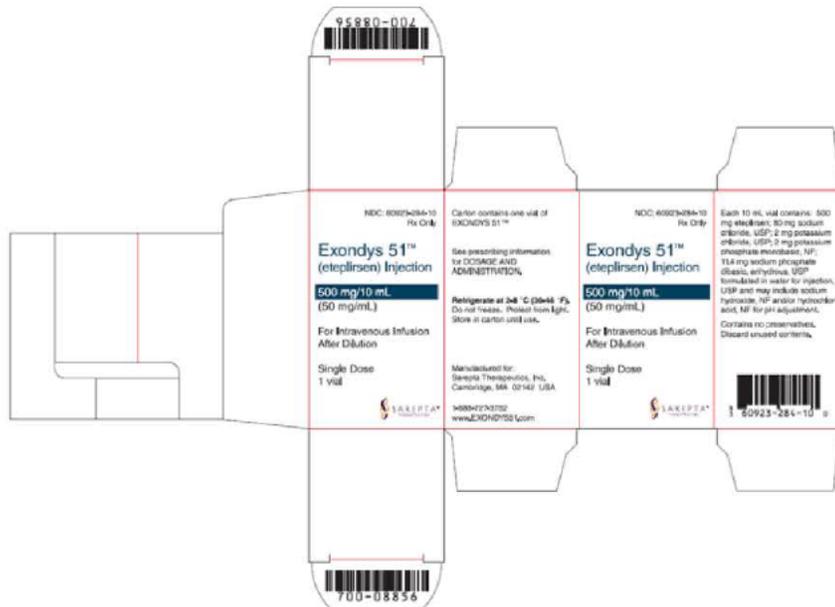
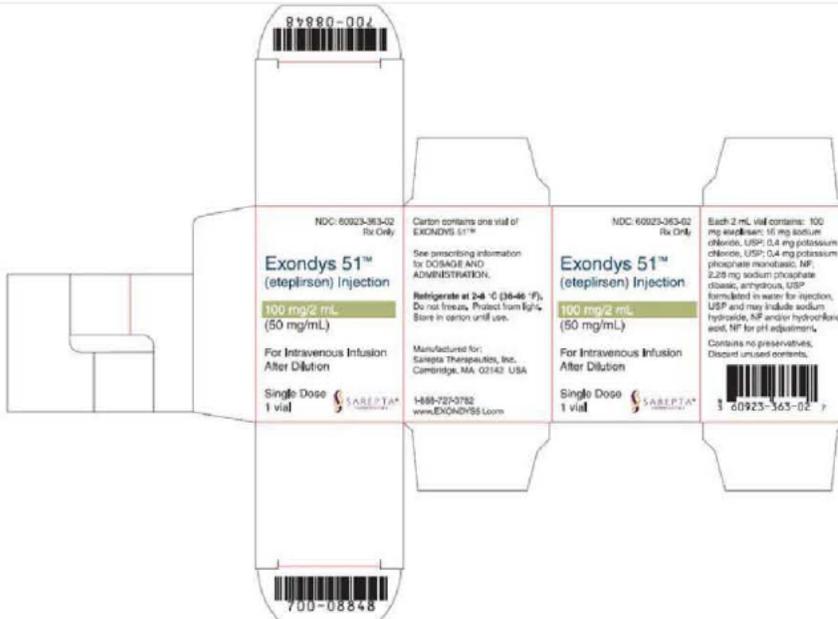
**Conclusion: Adequate**

*Based on the FDA’s recommendation, the sponsor revised the NDC code and replaced the ‘single use’ with ‘single dose’ on the labels.*

# QUALITY ASSESSMENT

NDA 206488

## 2) Carton Labeling



**NDA 206488**

*Reviewer's Assessment:*

<b>Item</b>	<b>Comments on the Information Provided in NDA</b>	<b>Conclusions</b>
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[ 201.10(a), 21CFR201.100(d)(2)]		Adequate
Sterility Information (if applicable)		Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate

**NDA 206488**

Item	Comments on the Information Provided in NDA	Conclusions
“See package insert for dosage information” (21 CFR 201.55)		Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	This statement is not listed. It is not required for an Rx.	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Adequate

**Conclusion: Adequate**

*Based on the FDA’s recommendation, the sponsor revised the NDC code and replaced the ‘single use’ with ‘single dose’ on the labels.*

**OVERALL ASSESSMENT AND SIGNATURES: LABELING**

**Reviewer’s Assessment and Signature:**

Based on the FDA’s recommendation, the sponsor made some revisions to the labeling. The labeling is adequate.

**Mariappan Chelliah, 21-Jan-2016**

**Secondary Review Comments and Concurrence: : I concur with Dr. Chelliah’s assessment and recommendation.**

**Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting), ONDP DNDP1/Branch 1  
January 25, 2016**

NDA 206488

**II. List of Deficiencies To Be Communicated**

Not applicable.

APPEARS THIS WAY ON ORIGINAL



## QUALITY ASSESSMENT



NDA 206488

### III. Attachments

#### A. Lifecycle Knowledge Management

##### a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/Site	H	Use of validated (b) (4) process (b) (4).	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/Equipment/Site	M	Control for endotoxins in (b) (4) drug substance and final product. Validated depyrogenation procedures for packaging components	Acceptable	
Assay (active), stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/Site	L	Additional risk for > 100% potency due to in-process (b) (4) identified during the review. Higher upper specification limit (115.0%) is allowable based on safety considerations.	Acceptable	Applicant has agreed to post-marketing commitment to revalidate the in-process (b) (4) and investigate root cause(s) for discrepancy between in-process (b) (4) results and batch release results (HPLC). Product specification to be reevaluated based on additional manufacturing experience.
Fill Volume/ Delivered Volume	Formulation Container Closure Process Parameters Scale/equipment/site	L	Monitored during filling process and tested at release.	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/site	L	Formulation is isotonic.	Acceptable	



### QUALITY ASSESSMENT



NDA 206488

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/site	L	Formulation is buffered to pH 7.5. Product is diluted with saline prior to infusion	Acceptable	
Particulate Matter	Formulation Container Closure Raw materials Process parameters Scale/equipment/site	M***	Tested at release and on stability.	Acceptable	
Leachable Extractables	Formulation Container Closure Raw materials Process parameters Scale/equipment/site	L	Container closure evaluated during product development.	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/site	L	Tested at release and on stability.	Acceptable	

\*Risk ranking applies to product attribute/CQA

\*\*For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc

\*\*\*Corrected from initial risk assessment Route of administration is intravenous, not subcutaneous

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VERIFICATION REPORT SUMMARY**

**TO:** Joseph Leginus, CMC Reviewer  
Mariappan Chelliah, CMC Reviewer  
Martha Heimann, CMC Lead  
Wendy Wilson-Lee, Ph.D., Branch Chief  
Youbang Liu, Ph.D., ONDP Methods Validation Project Manager  
Office of OMPT/CDER/OPQ/ONDP/DNDAPI/NDBII  
E-mail Address: joseph.leginus@fda.hhs.gov; Mariappan.Chelliah@fda.hhs.gov  
Phone: (301)-796-4102; (301)-796-1724

**FROM:** FDA  
Division of Pharmaceutical Analysis (CDER/OPQ/OTR/DPA)  
Michael E. Hadwiger, MVP Coordinator  
645 S Newstead Avenue  
St. Louis, MO 63110  
Phone: (314) 539-3811

**Through:** David Keire, Lab Chief, Branch 1  
Phone: (314) 539-3850

**SUBJECT:** Methods Verification Report Summary

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Application Number: 206488

Name of Product: Exondys 51 (eteplirsen), 50 mg/mL i.v.

Applicant: Sarepta Therapeutics

Applicant's Contact Person: Shamim Ruff, Vice President, Regulatory Affairs and Quality

Address: 215 First Street, Cambridge, MA 02142

Telephone: (617) 274-4009

Email: sruff@sarepta.com

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Date Methods Verification Consult Request Form Received by DPA: 8/31/2015

Date Methods Verification Package Received by DPA: 8/31/2015

Date Samples Received by DPA: 11/3/2015

Date Analytical Completed by DPA: 2/19/2016

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
645 South Newstead Ave.  
St. Louis, MO 63110  
Tel. (314) 539-3811

**Date:** February 25, 2016  
**From:** Cindy Ngo, Michael Hadwiger, Ph.D., Division of Pharmaceutical Analysis  
**Through:** David Keire, Ph.D., Lab Chief, Branch I  
**To:** Joseph Leginus, CMC Reviewer  
**Subject:** Sample Analysis of Exondys 51 (Eteplirsen) i.v. 50 mg/mL

**Link to analyst's data sheets:** <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c8c570>

**Background:** Sarepta Therapeutics, maker of Exondys 51, submitted a validation package which utilized liquid chromatography with ultraviolet detection (HPLC-UV) and mass spectrometric detection (HPLC-MS) for product characterization. DPA evaluated the following methods as shown in Table 1:

Table 1: Methods Evaluated

Method	Title	Analyte
3.2.S.4.3.1	Identification, Molecular Weight by LC/MS (ESI)	Drug Substance
3.2.S.4.3.3	Assay, Purity and Impurities by HPLC	Drug Substance
3.2.P.5.3	Identification, Molecular Weight by LC/MS (ESI)	Drug Product
3.2.P.5.3	Assay, Purity and Impurities by IP-HPLC (Binary Mobile Phase)	Drug Product
3.2.P.5.3	(b) (4) Impurity by SCX Chromatography	Drug Product

**Conclusion:**

The methods described in Table 1 are acceptable for use in quality control and for regulatory purposes. The results are summarized in Table 2 below.

**Summary of Analysis:** Summarized in Table 2.

Table 2: Analytical Results

Method	Acceptance Criteria	Result	Pass/Fail
3.2.S.4.3.1 Identification, Molecular Weight by LC/MS (ESI)	Molecular Weight 10305.7 (b) (4)	(b) (4)	Pass
3.2.S.4.3.3 Assay, Purity and Impurities by HPLC	Assay NLT 90%	(b) (4)	Pass
	Impurity (b) (4) NMT (b) (4)	ND	Pass
	Impurity (b) (4) NMT (b) (4) RRT= (b) (4) RRT= (b) (4)	(b) (4)	Pass
	Impurity (b) (4) NMT (b) (4)	(b) (4)	Pass
	Impurity (b) (4) NMT	ND	Pass
	Impurity (b) (4) NMT	(b) (4)	Pass
	RRT= (b) (4) RRT= (b) (4)	(b) (4)	Pass
	Impurity (b) (4) NMT (b) (4)	ND	Pass
	Impurity (b) (4) NMT	ND	Pass
	Impurity (b) (4) NMT	ND	Pass
	Total Impurities NMT (b) (4)	(b) (4)	Pass
	% Purity: NLT 94%	(b) (4)	Pass
3.2.P.5.3 Identification, Molecular Weight by LC/MS (ESI)	Molecular Weight: 10305.7 (b) (4) daltons	(b) (4)	Pass
3.2.P.5.3 Assay, Purity and Impurities by IP- HPLC	Assay: 90 – 110%	(b) (4)	Pass
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	RRT= (b) (4)	(b) (4)	
	RRT= (b) (4)	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Impurity (b) (4) Report Value	(b) (4)	
	Total Impurities NMT (b) (4)	(b) (4)	Pass
	% Purity: NLT 94	(b) (4)	Pass
3.2.P.5.4 (b) (4) Impurity by SCX Chromatography	Impurity (b) (4): RRT (b) (4); Report value (b) (4) RRT (b) (4) RRT (b) (4) RRT (b) (4) (b) (4), RRT (b) (4)	(b) (4)	Pass

NMT=No more than; NLT=No less than; ND = Not Detected; RRT=relative retention time

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/s/  
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MICHAEL E HADWIGER  
02/26/2016  
Final report NDA 206488

DAVID A KEIRE  
02/26/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Laura C. Pogue, Ph.D.**  
**645 S. Newstead Avenue**  
**St. Louis MO 63110**

**FROM:** Joseph Leginus, CMC Reviewer  
Mariappan Chelliah, CMC Reviewer  
Martha Heimann, CMC Lead  
Office of New Drug Products (ONDP)  
E-mail Address: Joseph.Leginus@fda.hhs.gov; Mariappan.Chelliah@fda.hhs.gov  
Phone: (301) 796-4102 (Joe); (301) 796-1724 (Mari)

**Through:** Wendy Wilson-Lee, Ph.D., Branch Chief  
Phone: (301)-796-1651

**and**

Youbang Liu, Ph.D., ONDP Methods Validation Project Manager Phone: (301)-796-1926:

**SUBJECT:** Methods Validation Request

---

Application Number: NDA 206488

Name of Product: EXONDYS 51 (eteplirsen) iv, 50 mg/mL

Applicant: Sarepta Therapeutics

Applicant's Contact Person: Shamim Ruff, Vice President, Regulatory Affairs and Quality

Address: 215 First Street, Cambridge, MA 02142

Telephone: (617) 274-4009 Email: sruff@sarepta.com

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Date NDA Received by CDER: 6/26/2015

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP:

Special Handling Required:

DATE of Request: August 31, 2015

DEA Class:

Requested Completion Date: 10/30/2015

**Format of Methods Validation Package (MVP)**

User Fee Goal Date: 2/26/2016

Paper  Electronic  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the A/NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the Methods Validation Requestor and the Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the Methods Validation Requestor and the Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The CMC Reviewer, Methods Validation Project Manager, and CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

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MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 206488
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				
Specifications/Methods for New Drug Substance(s)				
Specifications/Methods for Finished Dosage Form(s)				
Supporting Data for Accuracy, Specificity, etc.				
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: <b>REQUESTED DETERMINATIONS</b> Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
1.LC/MS (	1.Identification, Molecular Weight by I	3.2.P.5.3/p5	0	These methods are used for the I
2. (b) (4)	2.Assay, Purity and Impurities by (b) (4)	3.2.P.5.3/p9		
3.SCX Chromatography	3. Impurity (b) (4) by SCX Chromatography	3.2.P.5.3/p31		
LC/MS (ESI)	Identification, Molecular Weight by LC/MS (ESI)	3.2.S.4.3.1/ p. 6	0	These methods are used for the I
(b) (4)	Assay and Impurities by (b) (4)	3.2.S.4.3.3/ p. 28		

Additional Comments: **Note that this application is under priority review and therefore it has shorter timeline for 1**

### Methods Validation Request Criteria

<b>MV Request Category</b>	<b>Description</b>
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
<b>7</b>	Methods that are subject to a “for cause” reason

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/s/  
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DAHLIA A WOODY  
09/01/2015

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Application #: 206488	Submission Type: Original New Drug Application 505 (b) (1)	Established/Proper Name: Eteplirsen
Applicant: Sarepta Therapeutics	Letter Date: 26 June 2015	Dosage Form: Injection
Chemical Type: 1	Stamp Date: 26 June 2015	Strength: 50 mg/mL

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?		X	No <b>potential review</b> issues were identified during the filing review. However, information requests will be forwarded to the applicant.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Oligonucleotide drug substance

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment	
<b>Regulatory Considerations</b>					
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Eteplirsen adopted 2010	
21.	End of Phase 2/Pre-NDA Agreements	<input type="checkbox"/>	<input type="checkbox"/>	<p>October 17, 2013 End of Phase 2 meeting: Advice regarding drug substance and drug product specifications and analytical procedures, data needed to support comparability of clinical drug substance manufacturing process (A1) to commercial process (A2) given change in (b) (4) and streamlining of the (b) (4) process. Primary stability data for drug substance to be generated using A2 process drug substance. Flexibility with respect to product stability data since interval between manufacture and administration to patient initially expected to be approximately one month.</p> <p>September 3, 2014 CMC pre-NDA meeting: Agreement on starting materials. Advice regarding analytical procedures. Note that the official FDA minutes (09/08/2014) indicate the applicant was advised to “Test API powder with MALDI-TOF across all batches to show consistency of the impurity profile and monitor batch to batch consistency.” The intent of this advice was that the firm perform direct MALDI-TOF on historical batches, not as a routine release test. Refer to “Agency Correspondence – Pre-NDA Minutes Revision” located in Module 1.6.3.</p>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Proposed protocol applicable to multiple potential changes to drug substance manufacture.	
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Quality Considerations</b>					
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
27.	Design Space	Formulation		<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process		<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods		<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other		<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology <sup>1</sup>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients		<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial		<input type="checkbox"/>	<input checked="" type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Claim for categorical exclusion
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

<b>C. FILING CONSIDERATIONS</b>					
<b>FACILITY INFORMATION</b>					
3.	<p>Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Name of facility,</li> <li><input type="checkbox"/> Full address of facility including street, city, state, country</li> <li><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</li> <li><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</li> <li><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</li> <li><input type="checkbox"/> DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Manufacturing facility is a DMF
4.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Is a manufacturing schedule provided?</li> <li><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>DRUG SUBSTANCE INFORMATION</b>					
5.	<p>For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture                             <ul style="list-style-type: none"> <li><input type="checkbox"/> Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li><input type="checkbox"/> Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li><input type="checkbox"/> Includes complete description of product lots and their uses during development – BLA only</li> </ul> </li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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## FILING REVIEW

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance                             <ul style="list-style-type: none"> <li>o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> </li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability                             <ul style="list-style-type: none"> <li>o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> </ul>			
DRUG PRODUCT INFORMATION				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots</li> <li>o Includes complete description of product lots and their uses during development</li> </ul> </li> <li><input type="checkbox"/> Manufacture                             <ul style="list-style-type: none"> <li>o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> </li> <li><input type="checkbox"/> Control of Excipients</li> <li><input type="checkbox"/> Control of Drug Product                             <ul style="list-style-type: none"> <li>o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>o Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing</li> </ul> </li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	processes or facilities have occurred) <ul style="list-style-type: none"> <li>○ Analytical validation package for release test procedures, including dissolution</li> <li><input type="checkbox"/> Reference Standards or Materials</li> <li><input type="checkbox"/> Container Closure System                             <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> </li> <li><input type="checkbox"/> Stability                             <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> <li><input type="checkbox"/> APPENDICES</li> <li><input type="checkbox"/> REGIONAL INFORMATION</li> </ul>				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> <li>• Does the application contain the complete BA/BE data?</li> <li>• Are the PK files in the correct format?</li> <li>• Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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## FILING REVIEW

C. FILING CONSIDERATIONS					
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Provided for drug substance (not required) and one batch each of 2 mL and 10 mL filled vials.
16.	<p>Are the following information available in the Appendices for Biotech Products [3.2.A]?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> facilities and equipment                             <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing flow; adjacent areas</li> <li><input type="checkbox"/> other products in facility</li> <li><input type="checkbox"/> equipment dedication, preparation, sterilization and storage</li> <li><input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination</li> </ul> </li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:                             <ul style="list-style-type: none"> <li><input type="checkbox"/> avoidance and control procedures</li> <li><input type="checkbox"/> cell line qualification</li> <li><input type="checkbox"/> other materials of biological origin</li> <li><input type="checkbox"/> viral testing of unprocessed bulk</li> <li><input type="checkbox"/> viral clearance studies</li> <li><input type="checkbox"/> testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	<p>Are the following information available for Biotech Products:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:                             <ul style="list-style-type: none"> <li><input type="checkbox"/> LAL instead of rabbit pyrogen</li> <li><input type="checkbox"/> Mycoplasma</li> </ul> </li> </ul> <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>			<input checked="" type="checkbox"/>	

## OFFICE OF PHARMACEUTICAL QUALITY

### FILING REVIEW

#### Initial Risk Assessment for Eteplirsen Injection

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMECA RPN	Comment
Sterility	x Formulation x Container Closure x Process Parameters x Scale/Equipment/Site	4	5	5	100	Administered intravenous Potential failure modes – non-sterile units
Endotoxin Pyrogen	x Formulation x Container Closure x Process Parameters x Scale/Equipment/Site	2	4	4	32	Potential failure modes – Excessive Endotoxin Levels
Assay (active), stability	x Formulation x Container Closure x Raw Materials x Process Parameters x Scale/Equipment/Site	3	2	1	6	Potential failure modes – Degradation, Process Impurities Moderately stable drug
Uniformity of Dose – Fill Volume/Delivered Volume	x Formulation x Container Closure x Process Parameters x Scale/equipment/site	2	2	2	8	Potential failure modes – insufficient dose
Osmolality	x Formulation x Raw materials x Process parameters x Scale/equipment/site	2	3	2	12	Small volume parenteral Potential failure modes – irritation, edema Specification range 260 - 320
pH (High)	x Formulation x Container Closure x Raw materials x Process parameters x Scale/equipment/site	3	4	1	12	Target pH range 7.0 – 8.0 Potential failure modes – irritation, particulate formation (b) (4)

## OFFICE OF PHARMACEUTICAL QUALITY

### FILING REVIEW

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMECA RPN	Comment
Particulate Matter	x Formulation x Container Closure x Raw materials x Process parameters x Scale/equipment/site	3	3	3	27	Administered subcutaneous Potential failure modes – irritation, embolism
Leachable Extractables	x Formulation x Container Closure x Raw materials x Process parameters x Scale/equipment/site	2	4	3	24	Potential failure modes – generation of impurities
Appearance	x Formulation x Raw materials x Process Parameters x Scale/equipment/site	3	3	1	9	Potential failure modes – degradation, contamination

RPN < 25 is considered low risk

RPN 25 – 60 is considered moderate risk

RPN > 60 is considered high risk

Martha R.  
Heimann -S

Digitally signed by Martha R.  
Heimann -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300091  
527, cn=Martha R. Heimann -S  
Date: 2015.08.28 12:39:06 -04'00'