CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209531Orig1s000

CHEMISTRY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: December 15, 2016

TO: Nick Kozauer, M.D., Team Lead, Division of Neurology Products

THROUGH: Fannie Choy, R.Ph., Regulatory Project Manager

FROM: Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting), Office of New Drug Products

SUBJECT: Recommended Carton/Container Label Edits

APPLICATION/DRUG: NDA 209531 SPINRAZA® (nusinersen) Injection

Dr. Kozauer,

The Office of Pharmaceutical Quality (OPQ) held a teleconference with Biogen concerning additional recommended revisions to the carton/container labels for NDA 209531 on December 8, 2016, followed by an information request on December 8, 2016. The requested revisions were to:

1. Update the drug product carton label to include the expression of the active ingredient's strength; and,
2. Update the drug product expiration period when stored refrigerated in the commercial packaging to 30 months.

Biogen agreed to implement these changes on the next label printing and to submit the updated draft label as a CBE labeling supplement in a Quality Amendment to the NDA dated December 9, 2016 (SD 47). We note that the applicant's response is acceptable and OPQ will document this agreement in the appropriate section of the action letter.

Please feel free to contact me or Dahlia A. Woody, Regulatory Business Project Manager for OPQ if you have any questions.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 12/15/2016 11:42:24AM
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NDA/BLA > NDA 209531

NDA-209531-ORIG-1

Edit Project | Project Actions

Project Owner
Fannie (Yuet) Choy
Regulatory Project Manager

Status	Condition	Planned Completion	Percent Complete
Current	At Risk	Dec 23, 2016	72.8%

Project Summary | Project Details | Application Life Cycle | Application History | **Inspection View** | Tasks | More

As of Dec 23, 2016 9:57 am GMT

Inspection View

New Task | Export

Details | Summary

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)								
7	Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.	IM - Filing PM/Coordinator	7/7/16	9/22/16	Complete	Go to Form	
117	Overall Manufacturing Inspection Recommendation		Aditi Thakur	8/23/16	11/21/16	Complete	Go to Form	Recommendation: Approve
Parent: Facility: [redacted] (b) (4) | FACILITY STATUS: PENDING (1)								

Recommendation: APPROVAL

NDA 209531
Review #1

Drug Name/Dosage Form	Nusinersen Injection
Strength	2.4 mg/mL
Route of Administration	Intrathecal
Rx/OTC Dispensed	Rx
Applicant	Biogen, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S)
Original – Part 1 (SD 3)	09-AUG-2016	All
Amendment (SD 2)	09-AUG-2016	DS, DP, Facilities
Amendment (SD 4)	16-AUG-2016	DP
Amendment (SD 5)	19-AUG-2016	DP
Amendment (SD 6)	09-SEP-2016	DP, Micro
Original – Part 2 (SD 7)	23-SEP-2016	All
Amendment (SD 8)	26-SEP-2016	DS, DP, Micro
Amendment (SD 12)	03-OCT-2016	Process
Amendment (SD 18)	19-OCT-2016	DP
Amendment (SD 19)	21-OCT-2016	EA
Amendment (SD 20)	25-OCT-2016	DP
Amendment (SD 24)	26-OCT-2016	DS
Amendment (SD 27)	03-NOV-2016	Process
Amendment (SD 28)	04-NOV-2016	DS, DP, Facilities
Amendment (SD 31)	09-NOV-2016	Micro
Amendment (SD 33)	14-NOV-2016	DP
Amendment (SD 35)	16-NOV-2016	DS
Amendment (SD 39)	29-NOV-2016	DS, DP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	Branch 1/DNDAPI/ONDP
Drug Product	Mariappan Chelliah	Branch 1/DNDPI/ONDP
Process	Erin Kim	Branch VIII/DPAIII/OPF
Microbiology	Denise Miller	Branch II/DMA/OPF
Facility	Aditi Thakur	Branch II/DIA/OPF
Biopharmaceutics	Gerlie Geiser	Branch 1/DB/ONDP
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPMI/OPRO
Application Technical Lead	Wendy Wilson-Lee	Branch 1/DNDPI/ONDP
Laboratory (OTR)	Kui Yang	Branch II/DPA
ORA Lead	Caryn McNab	
Environmental Analysis (EA)	James Laurenson	EA/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	Type III		(b) (4)	N/A	No review	Adequate information provided in the NDA
	Type III			N/A	No review	Adequate information provided in the NDA
	Type V			Adequate	November 2015	Requalification scheduled for December 2016

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	10011	Nusinersen Injection (ISIS 396443)

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209531 for Spinraza® (nusinersen) Injection, 2.4 mg/mL for intrathecal administration. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4) and a 30 month drug product expiration period when stored refrigerated in the commercial packaging. The following comments represent post-approval quality agreements between Biogen, Inc. and OPQ and **should be included in the action letter**:

1) We would like to remind you of the following post-approval quality agreements included in the amendment dated November 29, 2016 (SD 39) :

   A) To provide the nusinersen (ISIS 396443) (b) (4) data (b) (4)

   B) To provide the drug substance melting point method validation data, numerical acceptance criteria with justification, and description of the analytical method (b) (4)

   C) To re-examine the (b) (4) drug substance acceptance criteria after data is generated from a total of (b) (4) commercial drug substance batches, including the (b) (4) process validation batches in the filing. Biogen will tighten the specifications to (b) (4)% if appropriate based on data. These results and a revised specification table, if warranted, should be submitted in a CBE-0 supplement.

   D) To conduct stability testing of the (b) (4) drug product process validation batches up to (b) (4) months and report the results per post-marketing reporting requirements (21 CFR 314.70).

2) In addition, we remind you of the following agreement made during the teleconference:

   A) To update the carton and container labels to include the salt equivalency statement on the next printing and to submit this change as a CBE labeling supplement.

3) Based on the review of the data provided and in accordance with ICH Q1E, we grant a (b) (4) month re-test period for the drug substance when stored (b) (4) in the commercial packaging and a 30 month drug product expiration period when stored refrigerated in the commercial packaging.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Spinal muscular atrophy
Duration of Treatment	Four loading doses on ~ (b) (4) followed by a maintenance dose once every 4 months
Maximum Daily Dose	Patients (b) (4) 12 mg (5 mL) (b) (4)
Alternative Methods of Administration	None.

Nusinersen is an 18-mer oligonucleotide, formulated as a solution for intrathecal administration via slow bolus injection in the treatment of spinal muscular atrophy (SMA). SMA overall is a debilitating, often fatal, disease that impacts a multitude of patients from newborns to adults and is the leading genetic cause of infantile death. SMA1 is the most severe form of the disease and is often fatal in neonates. There are no FDA-approved treatments for SMA. FDA granted fast track designation (November 2011), rolling review (August 2016), and expedited review (October 2016) to address this unmet medical need.

Factors critical to the OPQ evaluation of the submission were the route of administration (intrathecal), patient population (largely neonates, toddlers, and children), and the review timeline (expedited). As highlighted in the initial risk assessment, key review issues included 1) adequacy of the control strategy to ensure sterility and microbial quality; 2) physiologically-compatible pH, osmolality, and electrolyte composition; 3) characterization and control of the oligo sequence and impurities; 4) adequacy of the control strategy to mitigate particulate matter contamination; 5) potential for delamination of the immediate container closure (glass vial); and 6) adequacy of the process validation and quality systems at the manufacturing sites.

Based on the information provided in the submission and in response to information requests, OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. The control strategy provides adequate assurance of the sterility and microbial quality of the final product as demonstrated by successful process validation at both the (b) (4) manufacturing sites. The control strategy also provides adequate assurance of physiological compatibility of the product and minimal particulate matter contamination. OPQ will monitor post-marketing adverse event and field alert reports for any signals of incompatibility with the (b) (4) used in the formulation and for particulate matter contamination. Based on the product design, the risk of delamination of the glass vials is low. The applicant sufficiently characterized the oligo sequence and impurity profiles of the drug substance and drug product to support approval and agrees to continue improvement of the analytical methods associated with these attributes (see post-approval quality agreements 1A – 1C above). The applicant agreed to confirm the stability of drug product manufactured at the (b) (4) site post-approval (see post-approval quality agreement #1D above) and will incorporate the active moiety/salt equivalency

(b) (4) (see post-approval quality agreement #2A above). Therefore, OPQ recommends APPROVAL of NDA 209531 and grants a (b) (4) month re-test period for the drug substance when stored (b) (4) and a 30 month drug product expiration period when stored refrigerated in the commercial packaging.

B. Quality Assessment Overview

Drug Substance

The nusinersen drug substance (ISIS 396443) is a (b) (4)

The drug substance is stored (b) (4)

Drug Product

Nusinersen drug product for intrathecal injection is formulated at strength of 2.4 mg/mL. Nusinersen is an SMN2-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy. The drug product is given as a slow bolus injection to the intrathecal space without any dilution. It is supplied as single dose (12 mg /5 mL), sterile, isotonic solution in clear glass vials and free of preservatives. (b) (4)

(b) (4) will manufacture the commercial batches of nusinersen injection. The proposed specification for the drug product, together with controls for impurities in the drug substance and the (b) (4) manufacturing process are adequate to ensure that the critical quality attributes of this injection drug product are well controlled. The Applicant has provided batch data for the stability, engineering, and validation batches. The available batch data and stability data supports the proposed specification.

The Applicant has provided up to 24 months of long-term and six month of accelerated stability data for the registration batches. In addition, they have provided up to 9 months of long-term stability data for the validation batches from Patheon. The available stability data supports a s***helf-life of 30 months when stored under refrigeration***.

Process

The manufacturing process for the proposed product involves (b) (4)

Quality Microbiology

This is a sterile solution (b) (4). There are two manufacturing sites proposed. The drug product is formulated, (b) (4) filled into vials, stoppered, and sealed. The review included the validation studies supporting the (b) (4) drug product, the (b) (4) proposed facility. Deficiencies were not identified in the information provided. The validation information supporting the (b) (4). The recommendation from a quality microbiology perspective is to approve.

Biopharmaceutics

The measured pH and osmolality of the Ready-To-Use injectable solutions used in the pivotal Phase 3 clinical trial (CS3B) (manufactured using (b) (4)) were comparable to the proposed commercial drug product (manufactured using (b) (4)). Based on Tables 2, 3, 5 and 6 of 3.2.P.5.4 Batch Analyses, the pH of these RTU solutions at batch release ranged from (b) (4) The main difference among manufacturing Processes (b) (4) The PK of nusinersen in plasma and CSF following intrathecal injection of the drug product to pediatric SMA patients were characterized.

Facilities

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 209531 are found to be acceptable.

Environmental Assessment

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. Additional information (calculation of expected introduction concentration, description of any internal and external data on nusinersen degradation prior to and after excretion, discussion of the extent to which use and excretion of nusinersen complied with existing guidance such as NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, and a discussion

of the potential for interaction with aquatic organisms) was required from the applicant to support the claim, given the new molecular entity status and the relatively new class of drugs (synthetic oligonucleotides).

The data provided by the applicant demonstrated the likelihood of little or no environmental risk from nusinersen. The EIC of (b) (4) ppb is more than (b) (4) orders of magnitude below the 1 ppb categorical exclusion value. The calculation appears accurate and reasonable. The available data indicate that nusinersen is excreted in *de minimis* concentrations, and while some molecules could be sufficiently stable to remain whole following wastewater treatment, any interaction with aquatic organism is highly unlikely. Therefore, the categorical exclusion claim is appropriate for the anticipated amount of drug to be used.

C. Special Product Quality Labeling Recommendations

OPQ recommends that that the drug be administered within 4 hours of preparation, not the proposed (b) (4) hours as data demonstrating the inability of microorganisms to proliferate in the drug product over a (b) (4) hour time period was not provided. This recommendation was incorporated into the PI label for discussion during labeling negotiations.

D. Final Risk Assessment (see Attachment)

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ENVIRONMENTAL ANALYSIS

R Regional Information

Summary: 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. Additional information was required from the applicant to support the claim, given the new molecular entity status and the relatively new class of drugs (synthetic oligonucleotides). The provided information, as well as other information from the literature, was reviewed and the claim for a categorical exclusion from an EA was found to be acceptable.

Environmental Analysis

The applicant provided a claim for a categorical exclusion from an EA in accordance with 21 CFR Part 25.31(b). Specifically, the applicant claimed that the expected introduction concentration (EIC) for nusinersen would be lower than the 1 ppb categorical exclusion value. The required statement of no extraordinary circumstances, per 21 CFR 25.15(a), was included.

Given the new molecular entity status of nusinersen, and the relatively new class of drugs (synthetic oligonucleotides, SOs), FDA asked the applicant to support the claim and the statement of no extraordinary circumstances by providing, at a minimum:

1. The calculation for the expected introduction concentration (EIC) of nusinersen;
2. A description of any internal or external (e.g., literature) data on the degradation of nusinersen prior to and following excretion;
3. A discussion of the extent to which use and excretion of nusinersen would be in compliance with any existing guidance, such as the exemptions noted in the National Institutes of Health (NIH), 2016, NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html; and
4. A discussion of the potential for interaction with aquatic organisms, including via reverse transcription to complementary DNA and incorporated into the genome.

A summary of the applicant response to FDA is as follows.

1. The highest expected quantity of the drug substance to be produced in any of the next five years is (b) (4) kg, which converts to an EIC of (b) (4) ppb (<<1 ppb).
2. Intact nusinersen was the most abundant oligonucleotide detected in plasma (approximately (b) (4) %).

3. The excretion of nusinersen from patients into the environment is exempt from the NIH Guidelines, as nusinersen cannot replicate and is not designed to integrate into DNA.
4. There is no potential for nusinersen to interact with aquatic organisms. The targeted gene, SMN2, is only found in humans. Furthermore, based on its mechanism of action, there is no potential for nusinersen to interact with genes or mRNA in aquatic organisms.

FDA responded that item 2 did not address degradation post-excretion, to which the applicant provided data indicating that first, excretion is low ((b) (4) %) during the 24 hours after dosing and subsequent 24 hour periods. Furthermore, while no studies have been formally conducted to evaluate the stability of nusinersen following excretion, environmental degradation is expected to occur by a combination of physical (e.g., temperature), chemical (e.g., pH, soft metal ions, oxidation), and enzymatic mechanisms.

FDA also asked the applicant to provide references regarding the item 4 statement that the targeted gene, SMN2, is only found in humans, and whether there have been any attempts to find this gene in other organisms. The applicant provided data indicating that first, the combination of nusinersen's physical properties and enzymatic degradation (e.g., gut flora, gut and serum nucleases) prevents the intact molecules from being readily absorbed by non-pareteral routes of exposure such as ingestion. Second, the applicant provided a reference indicating that there is no potential for nusinersen to interact with aquatic organisms, as the target messenger ribonucleic acid (mRNA), SMN2, is only found in humans.

Reviewer's Assessment:

The EIC of (b) (4) ppb is more than (b) (4) 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. Also, the required statement of no extraordinary circumstances was provided. As noted above, no supporting information was provided (none is required), but given nusinersen is an NME and within a relatively new class of drugs, additional data was required and a detailed review of the 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 (b) (4) applications also were reviewed.

The data provided by the applicant demonstrated the likelihood of little or no environmental risk from nusinersen. Also:

1. A material safety data sheet (MSDS) for another (b) (4) product contains no substances known to be hazardous to the environment or that are not degradable in waste water treatment plants ((b) (4)).

2. To supplement the applicants claims about the NIH Guidelines, FDA also reviewed the Guidelines and found that 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), (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 (b) (4) nanograms per kilogram body weight. The subject (b) (4) appears to meet these criteria.

In conclusion, the available data indicate that nusinersen is excreted in *de minimis* concentrations, and while some molecules could be sufficiently stable to remain whole following wastewater treatment, any interaction with aquatic organism is highly unlikely. Therefore, the claim for a categorical exclusion from an EA is acceptable.

Reference:

(b) (4) Safety Data Sheet - RNA oligonucleotide, (b) (4)

Primary EA Reviewer Name and Date: James Laurenson, 11/22/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 11/23/2016

Michael Furness

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James Laurenson

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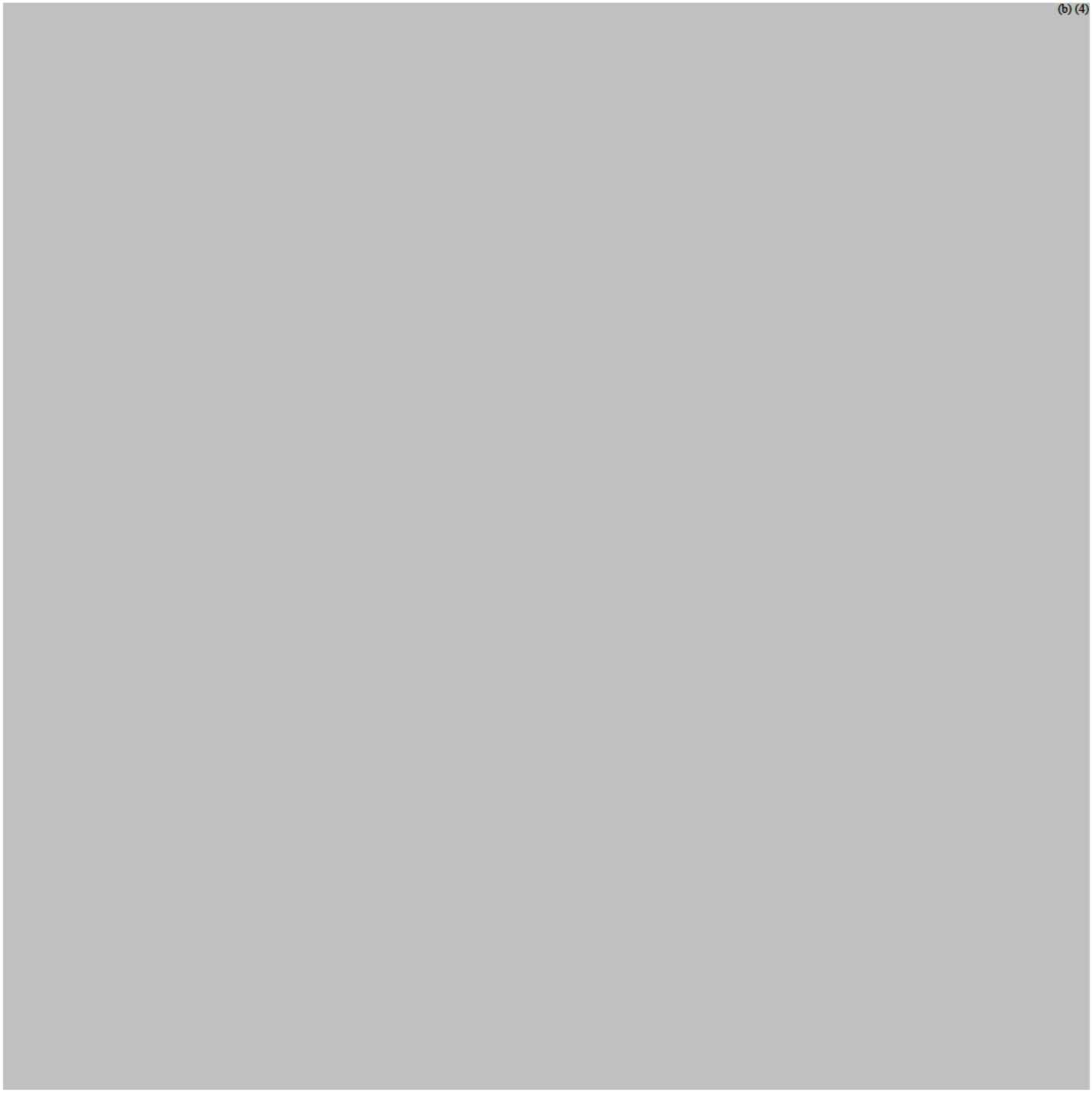
LABELING

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)



Reviewer's Assessment: Acceptable. The proposed carton label meets the regulatory requirement from a CMC perspective. During the review cycle, we edited the drug product strength under section 11 of the prescriber information to comply with the USP salt policy. However, a similar editing was not done to the carton labeling. While the carton labeling as cleared by the CMC is adequate for the safe dosage of the drug product, following the action on this NDA, we will ask the Applicant to revise the labeling to comply with the USP salt policy. Please see the deficiency comment below for the details of this proposed edit.

List of Deficiencies:

Please include the following labeling comment in the action letter:

The currently approved drug product carton label does not meet USP requirements for labeling the amount of active moiety and drug substance(Please refer to USP General Chapter <7> LABELING -- Amount of Active Moiety and/or Drug Substance per Dosage Unit). We ask that, before your next printing of the carton labels, you revise the drug product's composition statement on the fourth flap of the carton label as suggested below:

(b) (4)

You may submit your edited draft label as a CBE labeling supplement.

Primary Labeling Reviewer: Mariappan Chelliah (see below for date)

Secondary Reviewer: Wendy Wilson-Lee (see below for date)

Wendy Wilson- Lee

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Mariappan Chelliah

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MICROBIOLOGY

Product Background: The proposed drug product has an Orphan Designation (11-3367) for the treatment of spinal muscular atrophy (SMA). SMA is a serious condition that currently has no treatment other than supportive care. The application was granted a Fast Track designation in November 2011. Priority status was requested.

NDA: 209-531

Drug Product Name / Strength: Spinraza (nusinersen) Injection at 2.4 mg/mL

Route of Administration: Intrathecal bolus injection

Applicant Name: Biogen Inc.

Manufacturing Sites:

(b) (4)

Method of Sterilization: (b) (4)

Review Summary: This is a sterile solution that is (b) (4). There are two manufacturing sites proposed. The drug product is formulated, (b) (4) illed into vials, stoppered, and sealed. The review included the validation studies supporting the (b) (4) drug product, the (b) (4) vials, stoppers, and filling equipment (b) (4) at each proposed facility. Deficiencies were not identified in the information provided.

The recommendation from a quality microbiology perspective is to approve.

List Submissions being reviewed:

SD 0000, 0001 and 0002 submitted 09 August 2016

SD 0003 submitted 16 August 2016 (Response to Information Request)

SD 0004 submitted 19 August 2016 (Final section of a rolling submission)

SD 0007 submitted 26 September 2016 (Response to Information Request)

SD 0031 submitted 09 November 2016 (Response to Information Request)

Supporting References:

DMF (b) (4)

(b) (4)

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: NA

S Drug Substance

Reviewer's Assessment: The drug substance is (b) (4)

(b) (4)

P.1 Description of the Composition of the Drug Product

Description: The drug product is a single use, sterile, clear, and colorless isotonic solution for intrathecal administration. The fill volume is 5.0 mL. Batch size is (b) (4) L (approximately (b) (4) vials)

Composition: The composition is as follows in Table 1 (copied from Table 1 of application section 3.2.P.1).

Table 1: Composition of Drug Product

Table 1: Composition of Drug Product 2.4 mg/mL, 5.0 mL

Components	Quality Standards	Component Function	Nominal Quantity per 5.0 mL	Concentration (mg/mL)
ISIS 396443 (b) (4)	In-house	Active Ingredient	12 mg	2.4
Sodium (b) (4) phosphate dihydrate	USP, Ph.Eur., JPE	(b) (4)		0.05
(b) (4) phosphate, anhydrous[a]	USP, Ph.Eur., JPE			0.10
Sodium chloride	USP, Ph.Eur., JP			8.77
Potassium chloride	USP, Ph.Eur., JP			0.22
Calcium chloride dihydrate	USP, Ph.Eur., JP			0.21
Magnesium chloride hexahydrate	USP, Ph.Eur. JPC			0.16
1 N Sodium hydroxide solution	N/A[b]	pH adjustment	As needed	As needed
1 N Hydrochloric acid solution	N/A[c]	pH adjustment	As needed	As needed
Water for Injection	USP, Ph.Eur., JP	Vehicle	Q.S.	Q.S.
(b) (4)				

Q.S. = Quantity sufficient

Container Closure:

(b) (4)

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Neal Sweeney

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Denise Miller

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ATTACHMENT I: Final Risk Assessment

a) Drug Product: NDA 209531 Nusinersen Injection 2.4 mg/mL (Non-High Risk Drug)

From Initial Risk Identification			Review Assessment		
CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container closure Process/Scale Equipment/Site	High	Process validation (b) (4)	Acceptable	Confirm process qualification at next inspection of both (b) (4) manufacturing sites
Endotoxin Pyrogen	Formulation Container closure Process/Scale Equipment/Site	Medium	Process validation of (b) (4)	Acceptable	Confirm process qualification at next inspection of both (b) (4) manufacturing sites
Assay	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	In-process controls for drug substance (b) (4)	Acceptable	

QUALITY ASSESSMENT

From Initial Risk Identification			Review Assessment		
CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Physical stability	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	Formulated as a solution Recommended storage conditions mitigate degradation (b) (4)	Acceptable	
Uniformity of Dose (Fill/Delivered Volume)	Formulation Container closure Process/Scale Equipment/Site	Low	In-process controls for (b) (4)	Acceptable	
Osmolality	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	Formulated to simulate human CSF In-process controls for excipient charge amounts End product testing	Acceptable	Monitor AERS/FAERS for AE reports that may indicate incompatibility with aCSF used in formulation
pH	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	In-process control of (b) (4) End product testing	Acceptable	
Particulate matter	Raw materials Formulation Container closure Process/Scale Equipment/Site	Medium	In- proces (b) (4) End product testing Delamination risk assessment during development	Acceptable	Confirm low risk of delamination for any changes to glass vial

QUALITY ASSESSMENT

From Initial Risk Identification			Review Assessment		
CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Leachables/ extractables	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	Studies provided for both the processing equipment and container closure system	Acceptable	Confirm leachables/extractables profile for any change to processing equipment, processing conditions, container closure system, or storage condition
Appearance	Raw materials Formulation Container closure Process/Scale Equipment/Site	Low	In- process (b) (4) (b) (4) End product testing	Acceptable	