CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211172Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: October 1, 2018

TO: Fannie Choy, R.Ph., Sr. Regulatory Project Manager, Division of Neurology Products

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

SUBJECT: Product Quality Review of Quality-related Amendments

APPLICATION/DRUG: NDA 211172 Inotersen Injection 284 mg/1.5 mL

Ionis submitted amendments to the NDA with information relevant to product quality after closure of the OPQ IQA. These amendments were:

- Amendment SD 63 dated Sep. 27, 2018 – Revised Carton and Container Labels
- Amendment SD 61 dated Sep. 26, 3018 – Revisions to Module 3
- Amendment SD 64 dated Sep. 27, 2018 – Revisions to Module 3

The proposed revisions to the carton and container labels (Amendment 63) are acceptable from a product quality perspective as the proposed changes largely represented editorial or formatting changes to improve readability. DMEPA also found these revisions acceptable (see Label and Labeling Review Memo dated Sep. 27, 2018).

The proposed revisions to Module 3 (Amendment SD 64) are acceptable as they represent final updating of the submission to reflect changes/modifications agreed upon during the review cycle. Amendment SD 61 was submitted first (Sep. 26, 2017) but subsequently modified by Amendment SD 64 due to errors (inclusion of osmolality testing in Sections 2.3.P.8.2, 3.2.P.5.2, and 3.2.P.8.2). The Module 3 revisions included changes to:

- Street address correction for the [redacted] (b) (4) (revisions to Sections 3.2.P.7 and 3.2.R)
- Revisions to the drug substance and drug product specifications based on the responses to the Feb. 23, 2018 information request (revisions to Sections 2.3.S.7, 2.3.P.3, 2.3.P.5, and 2.3.P.8.2)
- Revisions to the analytical method descriptions and method validation information to reflect the current tests and specification limits (revisions to Sections 2.3.S.7, 2.3.P.3, 2.3.P.5, and 2.3.P.8.2)
- Revisions to the tests and specification limits throughout the eCTD to reflect final agreed upon regulatory specifications (revisions to Sections 2.3.S.7, 2.3.P.3, 2.3.P.5, and 2.3.P.8.2)

[redacted] (b) (4) All other revisions represent aligning Module 3 with previously submitted information and are acceptable from a product quality perspective.

Wendy
Wilson- Lee

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Recommendation: **APPROVAL**

NDA 211172
Review #01

Drug Name/Dosage Form	Inotersen Injection
Strength	189 mg/mL
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Ionis Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	06-NOV-2017	*Amendment*	07-MAR-2018
Amendment	25-JAN-2018	*Amendment*	03-APR-2018
Amendment	26-JAN-2018	*Amendment*	06-APR-2018
Amendment	29-JAN-2018	*Amendment*	12-APR-2018
Amendment	26-FEB-2018	*Amendment*	18-APR-2018

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rohit Tiwari/Charles Jewell	ONDP
Drug Product	Rao Kambhampati/Wendy Wilson-Lee	ONDP
Process	Kejun Cheng/Nallaperumal Chidambaram	OPF
Microbiology	Peggy Krieger/Erika Pfeiler	OPF
Facility	Kejun Cheng/Derek Smith	OPF
Regulatory Business Process Manager	Dahlia Walters	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP
Environmental	Rao Kambhampati/Raanan Bloom	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	III		(b) (4)	Not reviewed		Sufficient information in NDA
	V			Adequate	20-DEC-2017	
	III			Not reviewed		Sufficient information in NDA
	V			Adequate	11-APR-2018	
	V			Adequate	25-JAN-2018	
	V			Not reviewed		(b) (4)
	III			Adequate	18-APR-2018	
	V			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113968	Inotersen; ISIS 420915

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Complete	Approve	26-MAR-2018	J. Gertz

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 211172 for Inotersen Solution for Injection, 189 mg/mL.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Treatment of patients with hereditary transthyretin amyloidosis*** (b) (4)
Duration of Treatment	***Once-weekly (chronic)***
Maximum Daily Dose	(b) (4) ***based on dosing regimen***
Alternative Methods of Administration	***None***

Inotersen is a 2'-O-(2-methoxyethyl)(2'-MOE) antisense oligonucleotide developed for the treatment of hereditary transthyretin amyloidosis (hATTR) – a rare and fatal disease that causes mutations in the gene that codes for human transthyretin, a carrier protein for thyroxine and Vitamin A. Accumulation of amyloid deposits in multiple organ systems lead to a range of disease manifestations such as polyneuropathy, nephropathy, cardiomyopathy, and gastrointestinal dysfunction. Two major phenotypes exist (hATTR-PN and hATTR-CM) and are dependent on the organs impacted by the disease.

The Applicant received orphan drug designation in July 2012 and fast track designation in December 2012 for inotersen. Product quality related issues were discussed as part of a CMC-only Type C Written Responses Only meeting in July 2017. The drug product is regulated as a drug-device combination product.

Inotersen is formulated as a sterile solution for once-weekly subcutaneous injection, provided in a prefilled syringe. Key review issues included drug substance characterization; adequacy of the drug substance synthesis and control strategy; stability of the drug substance; sterility and stability of the drug product during manufacturing, at release, and over the proposed shelf-life; quality of the drug product for the proposed in-use period and condition; and characterization of the extractables/leachables profile for the primary packaging including potential exposure to (b) (4) functionality of the device; and potential for delamination of the glass syringe.

B. Quality Assessment Overview

Inotersen sodium is manufactured by the conventional (b) (4)

The inotersen drug substance is white to pale yellow solid and is freely soluble in aqueous environment. Inotersen sodium has phosphorothioate oligonucleotide backbone. (b) (4) The impurities in the inotersen drug substance are (b) (4) found to be acceptable by the P/T reviewer of this application. The inotersen sodium drug substance is stored (b) (4) **The inotersen sodium drug substance is stored (b) (4) and the initial retest period is set to (b) (4) months.**

The drug product is a sterile, preservative-free, aqueous solution of inotersen. Each 1.5 mL of the solution contains 284 mg of inotersen (which is equivalent to 300 mg of inotersen sodium). Formulation excipients include Water for Injection (WFI) and may include HCl and/or NaOH for pH adjustment to 7.5 to 8.5. The solution is clear and colorless to slightly yellow. The drug product solution is administered as a once weekly, single-use subcutaneous injection and no dilution is required prior to administration. The drug product is supplied in a glass prefilled syringe (PFS) with a staked needle and needle shield assembled into a Safety Syringe Device (SSD). The SSD consists of a (b) (4) (referred to as inotersen PFS in Safety Syringe Device). The device constituent parts of the combination product were found adequate by the CDRH reviewer. The drug product is supplied in cartons containing 1 or 4 prefilled syringes.

The proposed drug product specification is adequate to confirm the identity, assay, quality, and purity of the drug product. The CDRH device review found the device functional performance parameters to be adequate. Some of the acceptance criteria in the drug product specification were tightened by the applicant upon recommendation by the FDA. The three non-compendial analytical methods were described adequately and their validation reports are acceptable. Compatibility of the drug product solution with the packaging components was demonstrated. No extractables or leachables were identified from testing with the drug product contact materials of the primary container closure. Delamination of the glass syringe was not observed during drug product stability testing. Adequate stability data were provided for the drug product to support the proposed expiration dating period. **Based on the real-time stability data on three batches, an expiration dating period of 18 months is assigned when the drug product packages are stored refrigerated at 2-8ºC and protected from light. In addition, following**

distribution to the patients, the in-use shelf-life of 6 weeks is acceptable when the drug product is stored at up to 30ºC (86ºF) and protected from light.

The manufacturing process for this drug product (b) (4) [redacted] are acceptable. The release specification related to the microbiological tests is acceptable. The endotoxin limit for the drug product is acceptable. **All facilities listed are in good standing and acceptable.**

At the time of filing, it was determined that a Biopharmaceutics review was not needed for this submission. **The claim for a categorical exclusion from an environmental assessment in accordance with 21 CFR Part 25.31(b) and 25.15(d) is acceptable.**

C. Special Product Quality Labeling Recommendations (NDA only)

Based on the product quality review, the following labeling statements are recommended:

1. Store refrigerated (2-8^{o}C)
2. Protect from light
3. In-Use Period: Six weeks when stored up to 30^{o}C (86^{o}F), protected from light

D. Final Risk Assessment

Final Drug Product Risk Assessment

A. NDA 211172 Inotersen Injection, 189 mg/mL

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Sterility	Raw Materials Formulation Container Closure Process/Scale/Equipment Site	**High**	Adequate process, environmental, packaging, and testing controls ensure the sterility of the product	**Acceptable**	
Endotoxins/Pyrogens		**Medium**	Adequate process, environmental, packaging, and testing controls mitigate potential endotoxin contamination	**Acceptable**	
Assay		**Low**	Drug product long-term storage is refrigerated (b) (4) [redacted] End product testing	**Acceptable**	
Fill Volume/Deliverable Volume		**Low**	End product testing	**Acceptable**	
Osmolality		**Low**	Development studies demonstrate formulation and process consistently manufacture product within acceptable osmolality range	**Acceptable**	
pH		**Low**	End product testing	**Acceptable**	
Particulate Matter		**Medium**	End product testing	**Acceptable**	

QUALITY ASSESSMENT

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Leachables/Extractables	Raw Materials Formulation Container Closure Process/Scale/Equipment Site	**Medium**	Development studies showed no leachables or extractables of concern	**Acceptable**	
Appearance		**Low**	End product testing	**Acceptable**	
Device Functionality		**Medium**	Functional performance controls deemed adequate by CDRH	**Acceptable**	
Delamination		**Medium**	No evidence of delamination	**Acceptable**	

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Yes. Tegsedi™ (Inotersen)
Dosage form, route of administration	Yes. Injection, subcutaneous
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	284 mg inotersen (300 mg sodium salt)/ 1.5 mL in a single-dose, prefilled syringe including a safety syringe device (SSD)

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Yes. Detailed instructions were provided in package insert regarding dosing and administration and they are adequate from CMC perspective.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes. (b) (4) Injection in a single-dose prefilled syringe with safety syringe device (SSD)
Strengths: in metric system	Yes. 284 mg inotersen/1.5 mL solution
Active moiety expression of strength with equivalence statement (if applicable)	No. Per clinical division, equivalency statement is not included here.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes. Clear, colorless to pale yellow (b) (4) injection in a single-dose prefilled syringe with SSD.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes. Tegsedi™ (inotersen)
Dosage form and route of administration	Yes.
Active moiety expression of strength with equivalence statement (if applicable)	Yes.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Solution does not contain any excipients except WFI and, hydrochloric acid and/or sodium hydroxide for pH adjustment.
Statement of being sterile (if applicable)	Yes.
Pharmacological/ therapeutic class	Yes.
Chemical name, structural formula, molecular weight	Yes.
If radioactive, statement of important nuclear characteristics.	Not applicable.
Other important chemical or physical properties (such as pKa or pH)	Yes. pH was provided.

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: ***Adequate***
Overall the latest revised package insert complies with all the regulatory requirements from CMC perspective. Some modifications were suggested to the initial version and all those changes were implemented in the revised version.

II. Labels:

In the amendment dated 4/12/18 the applicant submitted the following revised container and carton labels, which reflect all the recommendations made by the ONDP and DMEPA reviewers.

1. ***Container and Carton Labels***

Immediate Container Label:

2. ***Carton Label***

(b) (4)

Carton Label (1 count):

(b) (4)

Carton Label (4-count):

Tray Cover Label:

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tegsedi™ (inotersen) Prominence of established name is less than 50% of the tradename.	Tegsedi™ (inotersen). Prominence of established name is less than 50% of the tradename.
Dosage strength	Yes.	Yes
Net contents	Yes.	Yes
"Rx only" displayed prominently on the main panel	No.	Yes
NDC number (21 CFR 207.35(b)(3)(i))	No	Yes
Lot number and expiration date (21 CFR 201.17)	No	Yes
Storage conditions	No	Yes
Bar code (21CFR 201.25)	No	Yes
Name of manufacturer/distributor	No	Yes
And others, if space is available		

Reviewer's Assessment of Labels: Adequate
The above labels include all the recommendations made by the ONDP and DMEPA reviewers. The above revised labels are acceptable from the CMC review

stand point. Since the pre-filled syringe label is small and all the information listed in the above table cannot be accommodated, the applicant included key information only. The remaining information was provided on the syringe tray cover label.

Overall Assessment and Recommendation: Acceptable.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 4/13//18.

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Rao Kambhampati

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Wendy Wilson- Lee

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MICROBIOLOGY

Product Background: FDA orphan and rare disease designations

NDA: 211172

Drug Product Name/ Strength: Inotersen (Tegsedi) Injection/189 mg/mL in a 1.5 mL prefilled syringe, single dose

Route of Administration: Subcutaneous

Applicant Name: Ionis Pharmaceuticals, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

***Review Recommendation*: Adequate**

***Review Summary*:** (b) (4)

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
11/6/17	11/6/17	N/A	11/8/17
1/4/18	1/4/18	N/A	N/A
1/25/18	1/25/18	N/A	N/A
1/26/18	1/26/18	N/A	N/A
3/7/18	3/7/18	N/A	N/A
4/3/18	4/3/18	N/A	N/A
4/6/18	4/6/18	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is in the eCTD format and has been granted priority review status. The 1/25/18 and 3/7/18 amendments are referenced for updated labeling information. The 1/26/18 amendment is referenced for updated quality information (stability, CCIT report, BD CoA). The 3/7/18 amendment is referenced for the response to the 2/23/18 CMC information request (IR) letter. The 4/3/18 and 4/6/18 amendments are referenced for responses to the CMC IR letter sent on 3/28/18. Some tables were copied from the application.

Concise Description Outstanding Issues Remaining: None identified

Supporting Documents:

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Clear, colorless to pale yellow solution
- **Drug product composition** –

Ingredient	Content per mL	Function
Inotersen, sodium salt	(b) (4) mg*	Active ingredient
Sodium hydroxide, 1 N	q.s.	Adjust pH
Hydrochloric acid, 0.3 N	q.s.	Adjust pH
Water for Injection	q.s.	(b) (4)

*equivalent to 189 mg inotersen

- **Description of container closure system** –

Configuration	Component	Description	Manufacturer
Prefilled syringe with 284 mg/1.5 mL in a 2.25 mL barrel	(b) (4)		

The primary container is a prefilled syringe (PFS), which is assembled into a secondary packaging safety syringe device (b) (4)

Reviewer's Assessment: Adequate

The description of the drug product and container closure system is satisfactory.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(b) (4)

Results:

(b) (4)

Reviewer's Assessment: Adequate

Notes to reviewer:

(b) (4)

Antimicrobial Effectiveness Testing

Reviewer's Assessment: N/A
The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacturing and quality control testing:

(b) (4)

Container closure integrity testing:

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(b) (4)

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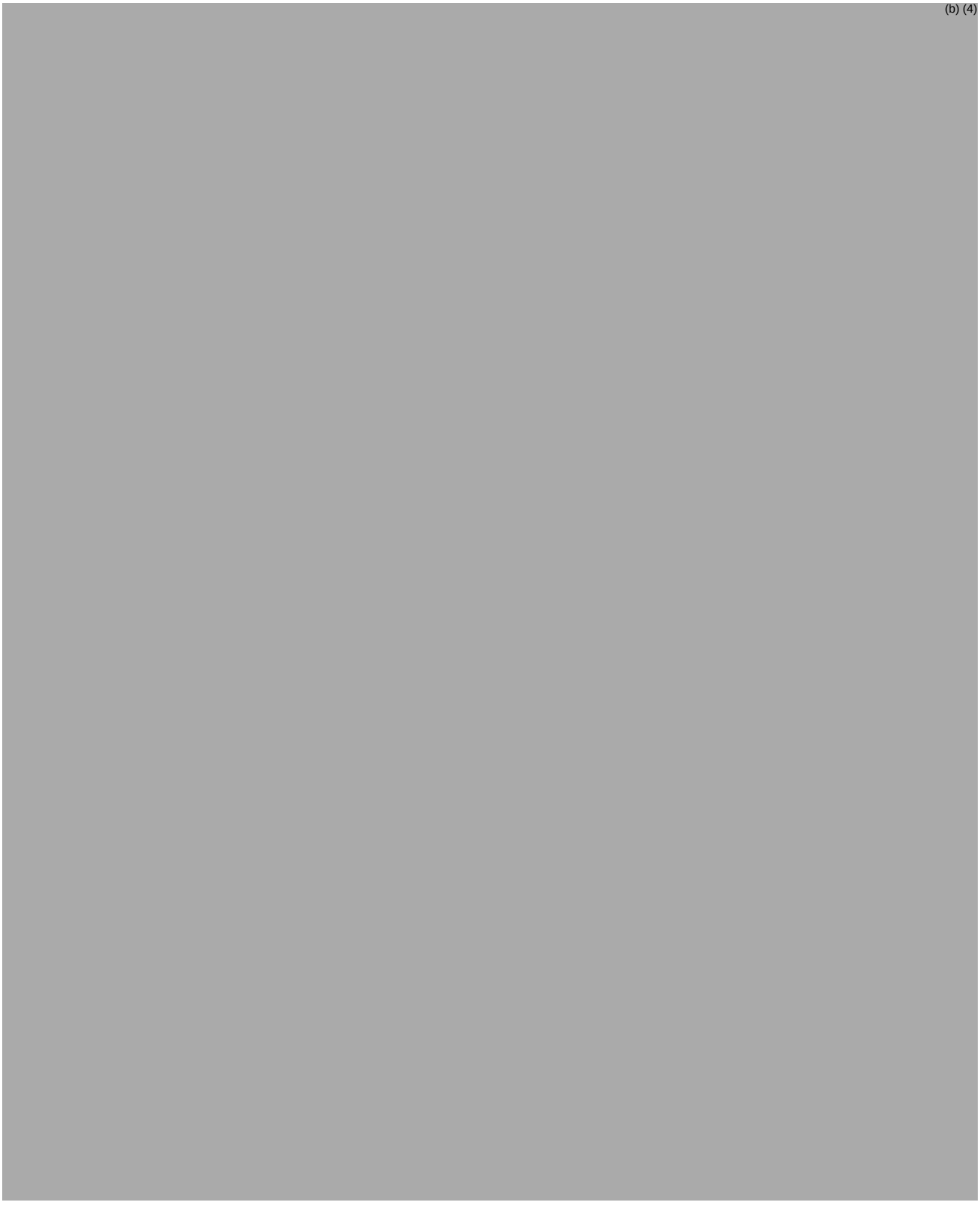
(b) (4)



P.5 Control of Drug Product

P.5.1 Specification

The product release specification includes the following microbiological tests:

Test	Test method	Acceptance criteria
Bacterial endotoxins	USP <85>	Not greater than (b) (4) EU/mL
Sterility	USP <71>	Conforms

Reviewer's Assessment: Adequate

The release specification related to the microbiological tests is acceptable.

Notes to reviewer:
1. It is noted in 3.2.P.5.6 that container closure integrity testing is not performed upon release.
2. A bacterial endotoxins acceptance criterion of NMT (b) (4) EU/mL was used for testing of early batches of product (3.2.P.5.4); the current criterion is in the table above.

P.5.2 Analytical Procedures – See P.5.1 and P.5.3
P.5.3 Validation of Analytical Procedures

Endotoxins
Test method: LAL kinetic chromogenic, according to USP <85>
Endotoxins specification: Not greater than (b) (4) EU/mL
USP Monograph limit: N/A
Drug potency: (b) (4) mg/mL
Lysate sensitivity: (b) (4) EU/mL
Calculated MVD (confirmed by reviewer): = (b) (4)

During verification of the test method, no inhibition or enhancement using a dilution of (b) (4) was shown. A dilution of (b) (4) will be used for routine testing.

Registration batch #(s) 017G16A, 018G16A and 019G16A were tested for bacterial endotoxins. Test results for prefilled syringes were (b) (4) EU/mL for 017G16A, (b) (4) EU/mL for 018G16A and (b) (4) EU/mL for 019G16A. Test results for fully assembled product were (b) (4) EU/mL for each batch. The results met the requirement.

Maximum adult dose according to the package insert: 284 mg in 1.5 mL

Calculated endotoxin dose at the proposed endotoxins specification and maximum dose - (b) (4)

The endotoxins dose at the proposed endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of (b) (4)

Reviewer's Assessment: Adequate

The endotoxin limit for the drug product is acceptable.

Notes to reviewer:
1. The drug product is not intended for pediatric use.
2. Clarification was requested about determination of the product dosage and endotoxins acceptance criterion. Also noted was that the package insert did not include instructions for adjustment of the dose per kg.

The following deficiency was issued in the 2/23/18 information request:

Deficiency: For bacterial endotoxins testing, conflicting information about the maximum dose of the drug product appears to be provided. A dose of 284 mg in 1.5 mL is noted in the package insert; however, it is stated in section 3.2.P.5.6 that a maximum dose of 6 mg/kg is administered, assuming a patient mass of 50 kg. With respect to calculation of the acceptance criterion for the bacterial endotoxins specification, we recommend using 70 kg as the standard for an adult. Please clarify the maximum dose to be administered and provide calculations showing the maximum possible endotoxins exposure.

Applicant's response (3/7/18 amendment): The proposed maximum dose is 284 mg of the free acid form of the drug/1.5 mL, which is equivalent to 300 mg of the sodium salt form of the drug. Assuming a patient weight of 50 kg, the 300 mg dose of the sodium salt form equates to a dose of 6 mg/kg. Calculation of endotoxin for the sodium salt form of the drug: (b) (4)

Note to reviewer: The applicant considers the use of 50 kg, instead of 70 kg, to be more conservative. If 50 kg is used in the calculation, exposure to endotoxin is still estimated to be under the recommended USP limit (b) (4)

Sterility
Test Method: (b) (4) according to USP <71>

Bacteriostasis/fungistasis testing was performed. One lot of the subject drug product in prefilled syringes was tested using a battery of compendial organisms. Inoculum counts were (b) (4) CFU. The subject drug product did not inhibit recovery of the test organisms.

Routine release testing is performed on prefilled syringes, before assembly with the safety device.

Registration batch #(s) 017G16A, 018G16A and 019G16A were tested for sterility. Samples were either prefilled syringes or fully assembled product; results conformed to requirements.

Reviewer's Assessment: Adequate

The method verification testing is satisfactory.

P.7 Container Closure - See P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

Proposed expiry: 18 months

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test method	Acceptance criteria
Bacterial endotoxins	USP <85>	Meets requirements
Container closure integrity	Dye ingress	Conforms

Stability storage conditions: 5°C/Ambient relative humidity, horizontal orientation

Test	Time (months)					
	Indicated commitment			(optional)		
	0	12	24	36	48	60
Bacterial endotoxins	X					X
Container closure integrity		X	X	X	X	X

Note to reviewer: The applicant states that if the study is terminated prior to the final scheduled time point, bacterial endotoxins and container closure integrity testing will be performed at the study terminating time point.

Post Approval Stability Commitment

The applicant commits to placing one of the current production lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot of assembled drug product will be added to the stability program.

Reviewer's Assessment: Adequate

Notes to reviewer:

1. The container closure testing acceptance criterion 'conforms' is noted in 3.2.P.5.6, p. 6, as no dye migration into the interior of the test system.
2. For stability testing, the applicant plans to use (b) (4) (from the 1/26/18 amendment, 1.2, response, p. 20), using method 17-011378-117235.01.
3. In 3.2.P.8, the post-approval commitment indicates that one current production lot will be placed into the stability program, instead of three. Further information will not be requested, as the drug product (chemistry) reviewer is satisfied that the sponsor has three commercial lots in the stability program and nine month stability data is provided.

P.8.3 Stability Data

Production scale batch #(s) 017G16, 018G16 and 019G16 were produced using the proposed commercial process. Samples were placed into stability studies (study 2) in the container closure system, including the (b) (4) The long-term stability testing protocol did not include bacterial endotoxins or sterility tests.

Samples from batch #(s) 017G16A, 018G16A and 019G16A (same batches as above, fully assembled product, study 3) were placed into long term stability studies, but the results provided do not include the first annual bacterial endotoxins and sterility tests.

Samples from batch #(s) 022H15B, 023H15B and 024H15B [redacted] were also placed into long term stability studies (study 1). The results for the 12 month timepoint were acceptable for bacterial endotoxins [redacted] EU/mL) and sterility (complies). Container closure testing was not noted.

Reviewer's Assessment: Adequate

A Appendices

A.2 Adventitious Agents Safety Evaluation

A.2.1 Materials of Biological Origin

A.2.2 Testing at Appropriate Stages of Production

A.2.3 Viral Testing of Unprocessed Bulk

A.2.4 Viral Clearance Studies

Reviewer's Assessment: N/A

R Regional Information

Executed Batch Records

(1.2, IR response, 3/7/18)

Registration/exhibit batch #(s) 017G16, 018G16 and 019G16, are numbered as 017G16A, 018G16A and 019G16A after assembly and packaging. The [redacted] batches are listed as 003K17 and 004K17, both with production dates of December 2017 and 005K17, production date in January 2018 (Table 6).

Reviewer's Assessment: Adequate

The blank proposed Master Batch Record appears to reflect the equipment and overall manufacturing set up for commercial production.

Comparability Protocols

Reviewer's Assessment: N/A. No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

Package Insert

Storage: Store at 2-8°C (36-46°F). May be stored at room temperature (< 30°C/86°F) for up to six weeks in the original carton. Protect from direct light.

Route of administration: SC

Container: Single dose

Post-dilution/constitution hold time - N/A

Reviewer's Assessment: Adequate

The labeling information is satisfactory related to sterility assurance.

Note to reviewer: The carton labels are labeled as sterile and single dose. The package insert states that the drug product is single dose.

Post-Approval Commitments
Reviewer's Assessment: N/A

***List of Deficiencies*:** None identified.

Primary Microbiology Reviewer Name and Date: Peggy Kriger, Ph.D., 4/18/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Erika Pfeiler, Ph.D.

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 4/27/2018 03:05:16PM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Peggy Kriger

Digitally signed by Peggy Kriger
Date: 4/27/2018 03:15:17PM
GUID: 534c169d00067f29cedbaa415df21ba2