CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218614Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 218614
Assessment # 1

Drug Product Name	TRYNGOLZA (Olezarsen) Injection
Dosage Form	Injection
Strength	80 mg/0.8 mL
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Ionis Pharmaceuticals, Inc.
US agent, if applicable	N/A
Proposed Indication(s) including Intended Patient Population	Treatment to reduce triglycerides
Duration of Treatment	N/A
Maximum Daily Dose	80 mg
Alternative Methods of Administration	None

Submission(s) Assessed (eCTD Sequence)	Document Date	Discipline(s) Affected
0001	04/19/2024	Quality (Original NDA submission)
0006	06/17/2024	Quality
0009	07/12/2024	Quality
0011	07/19/2024	Quality
0012	07/22/2024	Quality
0016	08/02/2024	Quality
0023	08/23/2024	Quality
0031	09/23/2024	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sa Wang	Daniel Jansen
Drug Product	Dan Berger	Mohan Sapru
Manufacturing	Krishna Ghosh	Sateesh Sathigari Vidya Pai
Microbiology	Jianli Xue	Nandini Bhattacharya
Environmental	Dan Berger	Mohan Sapru
Regulatory Business Process Manager	Oluwafunmike Ajomale	
Application Technical Lead	Akm Khairuzzaman	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs:** Acceptable.

DMF #	Type	Holder	Item Referenced	Status	Comments
(b) (4)	III		(b) (4)	Active	Sufficient information provided in the NDA
	V			Active	
	V			Active	
	V			Active	
	V			Active	
	III			Active	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

None

2. CONSULTS Yes

*CDRH was consulted for the device. CDRH reviewer, Drs. Farzaneh Akhavannik and Sruti Mistry concludes that the device constituent parts of this combination product are **approvable**.*

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 218614 is recommended for **approval**. As part of this action, an expiration period of 36 months for the product, stored under refrigerated condition at 2°C - 8°C (36° F to 46° F) in the commercial packaging, is granted.

II. SUMMARY OF QUALITY ASSESSMENTS

In accordance with section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, the Applicant, Ionis Pharmaceuticals Inc., submitted NDA 218614 to seek marketing approval for Tryngolza (Olezarsen) injection, 100 mg/mL. Olezarsen is a new synthetic conjugated antisense oligonucleotide. Its identity, purity, impurity, and manufacturing are adequately controlled through appropriate quality management system and validated analytical methods. The drug substance is stable for the intended storage period in its commercial packaging system. The new drug product is a subcutaneous injection, supplied as a sterile solution containing 100 mg/mL of olezarsen in a 0.8 mL pre-filled syringe (PFS) presentation assembled into an autoinjector that delivers a single dose of 80 mg olezarsen. It is formulated with compendial excipients such as water for injection, sodium chloride, (b) (4), sodium hydroxide, and hydrochloric acid. The components of the autoinjector, its engineering design, and functionality has been found to be adequate by the CDRH reviewers. The drug product manufacturing process including the device assembly, is adequately controlled by the quality management system of the listed cGMP compliant manufacturing facilities. From a quality perspective, the overall proposed control strategies are adequate to ensure consistent product quality regarding identity, strength, purity, potency, and stability.

A. Quality Assessment Overview

Drug Substance: Adequate

Olezarsen is a synthetic conjugated antisense oligonucleotide which appears as a white to yellow amorphous solid. It is hygroscopic and freely soluble in water. Its chemical structure is appropriately characterized using NMR, HRMS, sequence confirmation, stereochemistry, and elemental analysis. It appears as a white to yellow amorphous solid. It is hygroscopic and freely soluble in water. All physico-chemical properties are also adequately characterized to assure the identity and purity of the drug substance. The drug substance is manufactured using (b) (4). Its regulatory starting materials are adequately justified, controlled, and acceptable. Critical

manufacturing process parameters and proven acceptable ranges are established for each individual step. The name, structure, origin, fate, and control strategy of all oligonucleotide-related impurities are provided. The limits of specified impurities are supported by toxicological study and their level in specification is acceptable. No genotoxic or (b) (4) impurities are found in the drug substance. The specification of (b) (4) is also provided to ensure adequate control of the manufacturing process and support the quality of the drug substance. The drug substance quality control specification includes relevant tests such as appearance, identification, assay, purity, specified impurities, unspecified impurities, total degradation products, residual solvents, bacterial endotoxin, water content, and microbial limits. All analytical methods to control the quality of the drug substance are adequate and appropriately validated. Stability data support the proposed re-testing period of (b) (4) months when stored in commercial container at (b) (4) °C. For additional information, please refer to Drs. Sa Wang and Daniel Jansen' s review in Panorama dated 08/29/2024.

Drug Product: Adequate

Tryngolza (Olezarsen) injection is a sterile solution containing 100 mg/mL of olezarsen (supplied as 105 mg/mL of olezarsen sodium) in a 0.8 mL pre-filled syringe (PFS) presentation assembled into an autoinjector. The drug product is formulated (b) (4) (b) (4) injection (WFI) along with other compendial excipients such as sodium chloride, (b) (4), sodium hydroxide, and hydrochloric acid. There is no excipient of human or animal origin (b) (4) The commercial drug product formulation is identical with that of the Phase 3 trial product. The drug product packaging consists of 1 mL pre-filled syringes with Type (b) (4) glass barrels, stainless steel (b) (4) staked needles, and (b) (4) plungers. During the product development, critical quality attributes were identified, and they are adequately controlled by acceptable product specification which includes tests for appearance, degree of coloration, clarity and degree of opalescence, identification, sequence confirmation, mass, assay, purity, impurity, degradation products, pH, osmolality, particulate matter, bacterial endotoxin, sterility, container closure integrity, uniformity of dosage unit, device activation force, injection time, and deliverable volume. Extractables/leachables studies have confirmed the compatibility of the drug product with the commercial container closure. All analytical methods for quality control of this product are adequate and they are appropriately validated. Based on the provided stability data, a shelf-life of thirty-six (36) months is granted when stored under refrigerated condition at 2 °C – 8 °C (36 ° F to 46 ° F) in its original commercial packaging. For additional information, please refer to Drs. Dan Berger and Mohan Sapru' s review in Panorama dated 10/04/2024.

Labeling: Adequate

Updated labeling information is found to be adequate by the chemistry reviewer, Dr. Dan Berger. Minor edits were made in the chemistry section of the package insert.

Manufacturing: Adequate

The manufacturing process of Olezarsen 100mg/ml begins with (b) (4) (b) (4) (b) (4). The commercial batch size is approximately (b) (4) (b) (4). The manufacturing process reviewers, Drs. Krishna Ghosh and Sateesh Kumar Sathigari conclude that the overall manufacturing process is adequately controlled by appropriate control strategy, including in-process controls. For additional details, please refer to the manufacturing process review in Panorama dated 10/08/2024.

Biopharmaceutics: N/A

The drug product is an injectable solution. Therefore, biopharmaceutics is not relevant for this product.

Microbiology (if applicable): Adequate

Overall, the microbiological attributes of the drug product including its container closure integrity, bioburden (b) (4), sterilization/ depyrogenation (b) (4), closures, equipment and components, (b) (4) manufacturing process and its validation, in process controls, microbial analytical procedures and their validation are found to be adequate by the Microbiology reviewer, Drs. Jianli Xue and Nandini Bhattacharya. For additional details please refer to the microbiology review in Panorama dated 09/05/2024.

Manufacturing Facilities: Adequate

Based on the inspection (PAI), inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing, device assembly, and testing facilities concerning this NDA.

B. Risk Assessment: Overall quality risk is low.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Sterility	High	A sterile injectable formulation. Sterility is typically considered as high-risk attribute.	Low	(b) (4)
Endotoxin Pyrogen	Medium	A sterile injectable formulation. Endotoxin level for subcutaneous injection is typically considered as medium risk attribute.	Low	
Assay (API), stability	Medium to Low	Complex DS chemistry (antisense oligonucleotide)	Low	
Degradation impurities	Medium to low	Complex DS chemistry (antisense oligonucleotide)	Low	
Content Uniformity	Low	Homogeneous solution	Low	
Leachable extractables	Low	The container closure system (CCS) was qualified following the recommendations in USP <1661>, and extractables/ leachables testing per USP <1663>, USP <1664>, and the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiative for Parental Products and Ophthalmic Products. Subject to review.	Low	
pH	Low	Small volume parenteral product. Controlled as per the specification with appropriate limit.	Low	
Dosing efficiency/Dosing variability/Delivered dose	Low	A single dose pen presentation. The following tests are in place to ensure dosing accuracy: (i) injection activation force (ii) uniformity of dosage unit by weight variation, and (iii)delivered volume. With all three controls in place, the risk is low.	Low	

C. List of Deficiencies for Complete Response:
None

Application Technical Lead Name and Date:

Akm Khairuzzaman, Ph.D. 10/09/2024

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Following edits made to sections 11 for excipient function and 16 for storage information, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRYNGOLZA	Adequate
Established name(s)	Olezarsen	Adequate
Route(s) of administration	Injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	80 mg/0.8 mL in a single-dose autoinjector	Product strength expressed in terms of the active moiety per USP salt policy is adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose autoinjector	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Remove the single-dose autoinjector from the refrigerator 30 minutes prior to the injection and allow to warm to room temperature.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	80 mg/0.8 mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	80 mg/0.8 mL (refers to olezarsen free acid)	Adequate per the USP Salt Policy
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless-to-yellow solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRYNGOLZA, olezarsen	Adequate
Dosage form(s) and route(s) of administration	Single-use autoinjector.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Contains 80 mg olezarsen (equivalent to 84 mg of olezarsen sodium)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Disodium hydrogen phosphate, sodium chloride, sodium dihydrogen phosphate to maintain pH and provide tonicity, water for injection. May include hydrochloric acid and/or sodium hydroxide to adjust pH	Adequate after editing to add ingredient functions.
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	See list of inactive ingredients above.	Adequate. Quantities of pH & tonicity adjusting excipients are not required.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ Therapeutic class	Inhibitor of Apolipoprotein C-III (apoC-III) production	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{296}H_{419}N_{71}O_{154}P_{20}S_{19}Na_{20}$, 9124.48 Da.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Freely soluble in water and phosphate buffer.	Adequate

* DNA, d(P-thio) ([2′-O-(2-methoxyethyl)] rA-[2′-O-(2-methoxyethyl)] rG-[2′-O-(2-methoxyethyl)] m5rC-[2′-O-(2-methoxyethyl)] m5rU-[2′-O-(2-methoxyethyl)] m5rU-m5C-T-T-G-T-m5C-m5C-A-G-m5C-[2′-O-(2-methoxyethyl)] m5rU-[2′-O-(2-methoxyethyl)] m5rU-[2′-O-(2-methoxyethyl)] m5rU-[2′-O-(2-methoxyethyl)] rA-[2′-O-(2-methoxyethyl)]m5rU), 5′-[26-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[6-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]hexyl]amino]-3-oxopropoxy]methyl]-8,12,19-trioxo-16-oxa-7,13,20-triazahexacos-1-yl hydrogen phosphate], sodium salt (1:20).

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection (single-dose autoinjector)	Adequate
Strength(s) in metric system	80 mg/0.8 mL	Adequate
Available units (e.g., bottles of 100 tablets)	Single-dose autoinjector: 80 mg/0.8 mL	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Sterile, preservative-free, clear, colorless to yellow solution, NDC 71860-101-01.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose autoinjector	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not freeze. Do not expose to heat. Protect from light.	Adequate after edits.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Adequate after modification to: Store … between 2°C and 8°C (36°F and 46°F) in the original carton. Additionally specifying a room temperature storage range between 15°C and 30°C (59°F and 86°F) for up to 6 weeks.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by Ionis Pharmaceuticals Inc., Carlsbad, CA 92010	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Storage conditions, handling instructions and inactive ingredient list are provided in the Patient Information and Instructions for Use. After inclusion of edited storage conditions, this information complies with all regulatory requirements from a CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Autoinjector

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about autoinjector and carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TRYNGOLZA (olezarsen)	Adequate
Dosage strength	80 mg/0.8 mL	Adequate
Route of administration	Injection for subcutaneous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each (b) (4) contains 80 mg olezarsen (equivalent to 84 mg olezarsen sodium)	Adequate
Net contents (e.g. tablet count)	80 mg/0.8 mL solution	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	71860-101-01	Adequate
Lot number and expiration date	Not clearly marked on carton	Adequate after DMEPA recommended edits.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store refrigerated at 2°C to 8°C (36°F to 46°F). Can be stored at room temperature (b) (4) (b) (4).	Adequate based on recommended edits included in a comment for the PI storage conditions section 16.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose (b) (4)	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate, after recommendations by DMEPA.

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Distributed by Ionis Pharmaceuticals Inc., Carlsbad, CA 92010	Adequate
Medication Guide (if applicable)	Patient information contains storage conditions and inactive ingredients.	Adequate with edits to align with the PI.
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, its difference shall be plainly stated on its label.	NA	NA
Additional carton labeling comment		

Assessment of Carton and Container Labeling: *Adequate*
Required edits for storage information, bar code, lot # and expiration date have been addressed by comments in Section 16 of the prescribing information and by DMEPA. With the required edits, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All edits to the carton and container labels have been completed or are currently addressed. The Prescribing Information, Patient Information, Instructions for Use and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger, Ph.D. October 4, 2024

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

Mohan Sapru, Ph.D. October 4, 2024

Dan Berger

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Date: 10/04/2024 10:12:57AM
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Mohan Sapru

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	218614
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Olezarsen/100 mg/ml
Route of Administration	Subcutaneous
Applicant Name	Ionis Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DDLO
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original submission	4/19/2024
IR response	6/17/2024
Quality submission	7/19/2024
Quality submission	8/2/2024
IR response	8/23/2024

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: Microbiology review (b) (4) (adequate) dated (b) (4)

S DRUG SUBSTANCE

Assessment: ***Adequate***

The drug substance is not procured sterile. The API is (b) (4) (b) (4) at the proposed drug product manufacturing facility. Therefore, microbiology review will not be conducted for drug substance.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Sterile single-dose, ready-to-use clear, colorless to yellow solution for injection for subcutaneous administration.

- **Drug product composition –**

Table 1: Quantitative Composition of Olezarsen Solution for Injection, 80 mg

Ingredients	Quality Standards[a]	Quantity per Autoinjector	Quantity per Unit Dose (0.8 mL)	Function
Olezarsen[b]	Professed[b]	(b) (4)	80 mg as free acid (equivalent to 84 mg as sodium salt)	Active
Sodium dihydrogen phosphate (b) (4)	USP		(b) (4)	(b) (4)
Disodium hydrogen phosphate (b) (4)[c,e]	USP			
Sodium chloride	USP			
Hydrochloric acid[f]	NF			pH adjustment
Sodium hydroxide[f]	NF			pH adjustment
Water for Injection (WFI)	USP			(b) (4)

[a] USP - United States Pharmacopoeia; NF- National Formulary
[b] Olezarsen drug substance is supplied as a sodium salt. The label claim is expressed as the free acid concentration.
[c] (b) (4)
[d]
[e]
[f]
[g]
[h] To ensure no less than 0.8 mL is dosed upon injection, a (b) (4) mL target overfill is added.

- **Description of container closure system –** The drug product is packaged in a 1 ml long (1 ml L) staked needle glass prefilled syringe (PFS) closed with a (b) (4) rubber plunger stopper. The PFS is assembled into an autoinjector for the final drug product presentation.

Table 1: Description of Primary Packaging Components

Component	Description	[redacted]	Supplier/ Manufacturer
Syringe[a]	1 mL [redacted] glass, [redacted] clear, compliant with USP <660>, with 27G 1/2" special [redacted] bevel stainless steel needle and a rigid needle shield [redacted]	[redacted]	[redacted]
Rubber Plunger Stopper[a]	[redacted] rubber, [redacted] grey, compliant with USP <381> (physicochemical tests) [redacted]	[redacted]	[redacted]
	[redacted] rubber, [redacted] grey, compliant with USP <381> (physicochemical tests) [redacted]	[redacted]	[redacted]

[a] The rubber closure parts [redacted] In addition, [redacted] is used in the manufacture of these parts.

Exhibit batches # [redacted]* (PPQ batches, 7/19/2024 submission) *Different names used for the PPQ batches, see the table below.

Table 6: Overview of Autoinjector Process Performance Qualification

Details of PPQ Batches	Process Performance Qualification Batch Details		
Ionis AI Batch Number	CP678354-015-AI-A	CP678354-016-AI-A	CP678354-017-AI-A
[redacted]			
Ionis PFS Batch Number	CP678354-015	CP678354-016	CP678354-017
[redacted]			

Clinical/registration stability batch# CP678354-005, CP678354-006 and CP678354-007 (8 L)
Proposed commercial batch: [redacted] (p. 23/293, 1.11.1, 7/19/2024 submission)

Assessment: ***Adequate***

The sponsor provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DPMA IV
9/3/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya
CDER/OPQ/OPMA/DPMA II
9/3/2024

Jianli Xue

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Date: 9/05/2024 06:14:57AM
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Nandini Bhattacharya

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	9/30/2024		
To:	Oluwafunmike Ajomale FDA/OC/CDER/OPQ/OPRO/DRBPMIII/		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Farzaneh Akhavannik OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	Shruti Mistry, Injection Team OPEQ/OHT3/DHT3C		
Subject	Device engineering review consult for the new NDA 218614		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 9/12/2024 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 9/30/2024 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 218614
Sponsor	Ionis Pharmaceuticals, Inc
Drug/Biologic	Olezarsen
Indications for Use	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS)
Device Constituent	Auto-Injector
Related Files	Facilities Review for NDA 218614 (ICCR#00988361)

Review Team		
Lead Device Reviewer	*Farzaneh Akhavannik*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			The firm has provided adequate description of the device constituent.
Labeling	x			The firm has provided adequate labeling information.
Design Controls	x			The firm has provided adequate design controls documents.
Risk Analysis	x			The firm has provided adequate risk analysis documents.
Design Verification	x			Design verification review is performed through performance verification and validation testing. The provided testing is acceptable.
Consultant Discipline Reviews			x	This priority review is limited to engineering performance of the device constituent. Therefore, no discipline specific consults are requested.
Clinical Validation			x	This priority review is limited to engineering performance of the device constituent. The clinical validation review is deferred to CDER.
Human Factors Validation			x	This priority review is limited to engineering performance of the device constituent. The human factors review is deferred to CDER.
Facilities & Quality Systems			x	A facilities review was previous performed. Please see the facilities review memo dated 07/25/2024 (ICCR00988361).

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

Comment #: I have reviewed the performance of the Device design verification, Device Performance Data and Device release and stability data as requested in the clarification of consult request email dated August 20, 2024, as this is an expedited engineering review. The provided information regarding the device EPRs and performance verification of the device EPRs post aging and handling is acceptable, however, I also reviewed the risk analysis and quality systems data and identified some deficiencies related to lack of complete information provided. Risk analysis is important so we can understand the risk of the product, device constituent, and how the sponsor has mitigated them. The cGMP data and CAPA investigation information is important in verifying the sponsor's procedures and controls to ensure the continued conformance of the device design and performance specifications with the applicable standards and is required per 21 CFR 820, subpart I, K and J. I contacted consult RPM regarding the issue of IR deficiencies to be communicated with the sponsor on September 11, 2024, at which time she contacted, the CMC team who stated there is not enough time in their review clock for IR deficiencies. Therefore, CR deficiencies were issued. However, the CDER review team

communicated the deficiencies as IR after CDRH mid-cycle review was completed. The following IR deficiencies were issued:

1. (b) (4)

Reviewer's notes:

The sponsor has provided the device system FMEA which identified hazards and provides mitigations/controls for the identified hazards and verification of risk controls to reduce the identified risks to health. System failure modes, along with their end effects, are evaluated for the olezarsen combination product and is documented in Attachment 1 of the System FMEA ((b) (4)). Risk Controls have been identified for all failure modes within this System FMEA in order to reduce the probability of occurrence as low as possible. All failure modes that can result in a hazardous situation are rolled-up to the Hazard Analysis in order to ensure the Hazard Analysis provides a complete list of hazards, hazardous situations, and sequence of events, and that the risk of those hazards is assessed and controlled. The provided FMEA outlines appropriate hazards and mitigations for the device type.

The sponsor also provided the USE FMEA for ISIS 678354 for the Olezarsen Autoinjectors. The user FMEA documents the use error analysis for the development of the autoinjector, which includes the identification of use errors, potential effects, and related hazards/hazardous situations. The table below shows a summary of the critical tasks from the task analysis:

(b) (4)

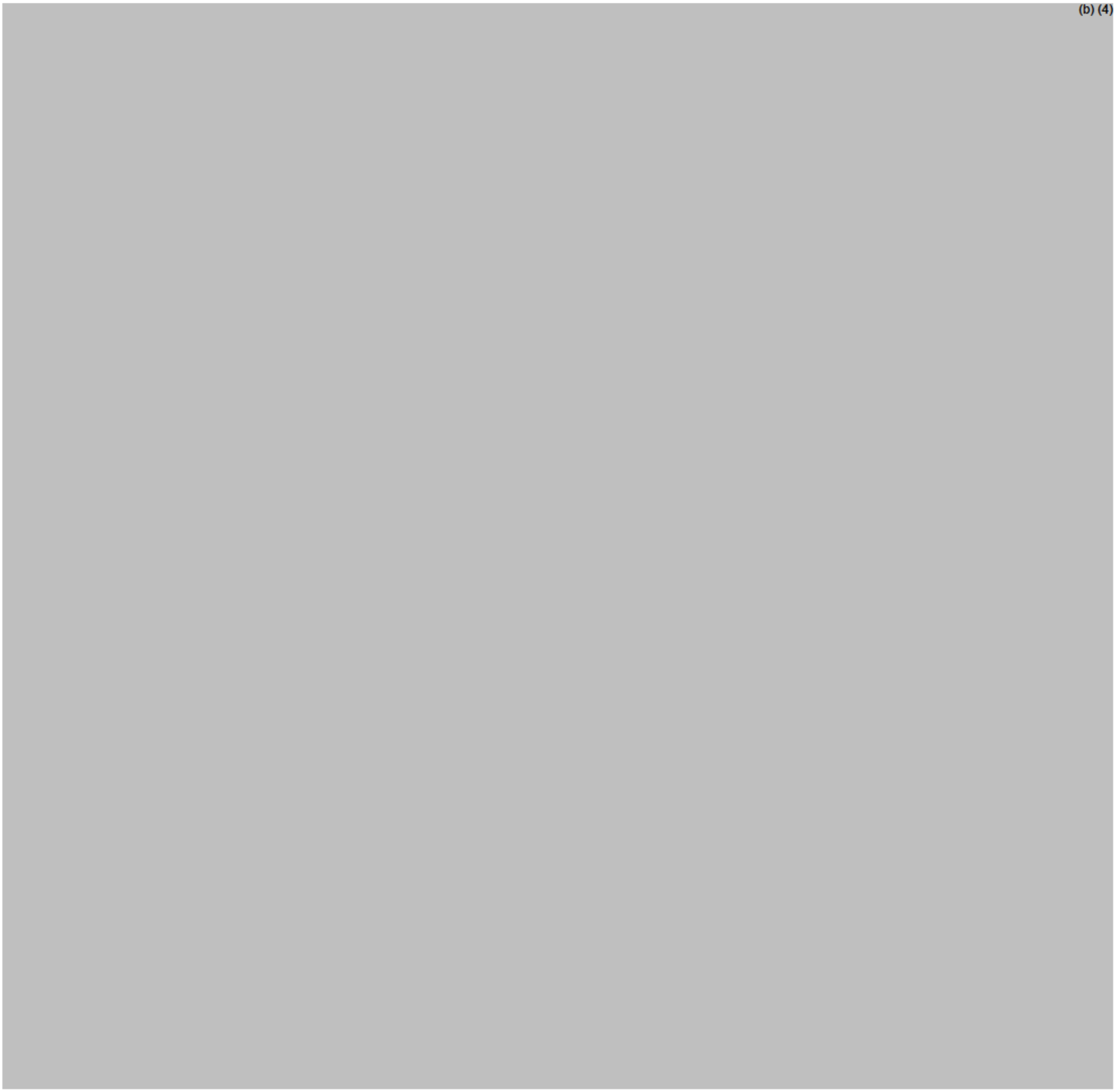
A Use FMEA table is also provided which adequately summarizes the analysis the use errors and potential foreseeable misuse along with their resultant effects. Please refer to Attachment 1 of document VV-QUAL-25847.

The third document provided is the Hazard analysis document for the autoinjector. The hazard analysis entails identifying hazards from possible occurrences or "hazardous effects". These hazardous events could stem from the environment or from human factors considerations during development of the olezarsen autoinjector, which included Risk Analysis, Risk Evaluation, and Risk Control. The hazard analysis is summarized in Attachment 1-Hazard analysis Table/Risk control Table (VV-QUAL-25621). The provided hazard analysis table adequately identified the potential hazards, their associated risk analysis, risk evaluation and risk control measures.

The individual risk controls are captured in the Risk Controls tab in Attachment 1, allowing reuse across multiple sequence of events. The Risk Controls tab identifies how each risk control has been implemented, the evidence of effectiveness of the risk control, and whether the risk control may result in a sequence of events associated with existing or new hazards or hazardous situations. Risk controls have been implemented in the form of design and labeling requirements, and affected sequence of events and Probability of sequence of events were evaluated and modified, if necessary, for the identified hazardous situations. The risk control table is complete and adequately describes reasonable controls for the identified hazards.

2. (b) (4)

(b) (4)

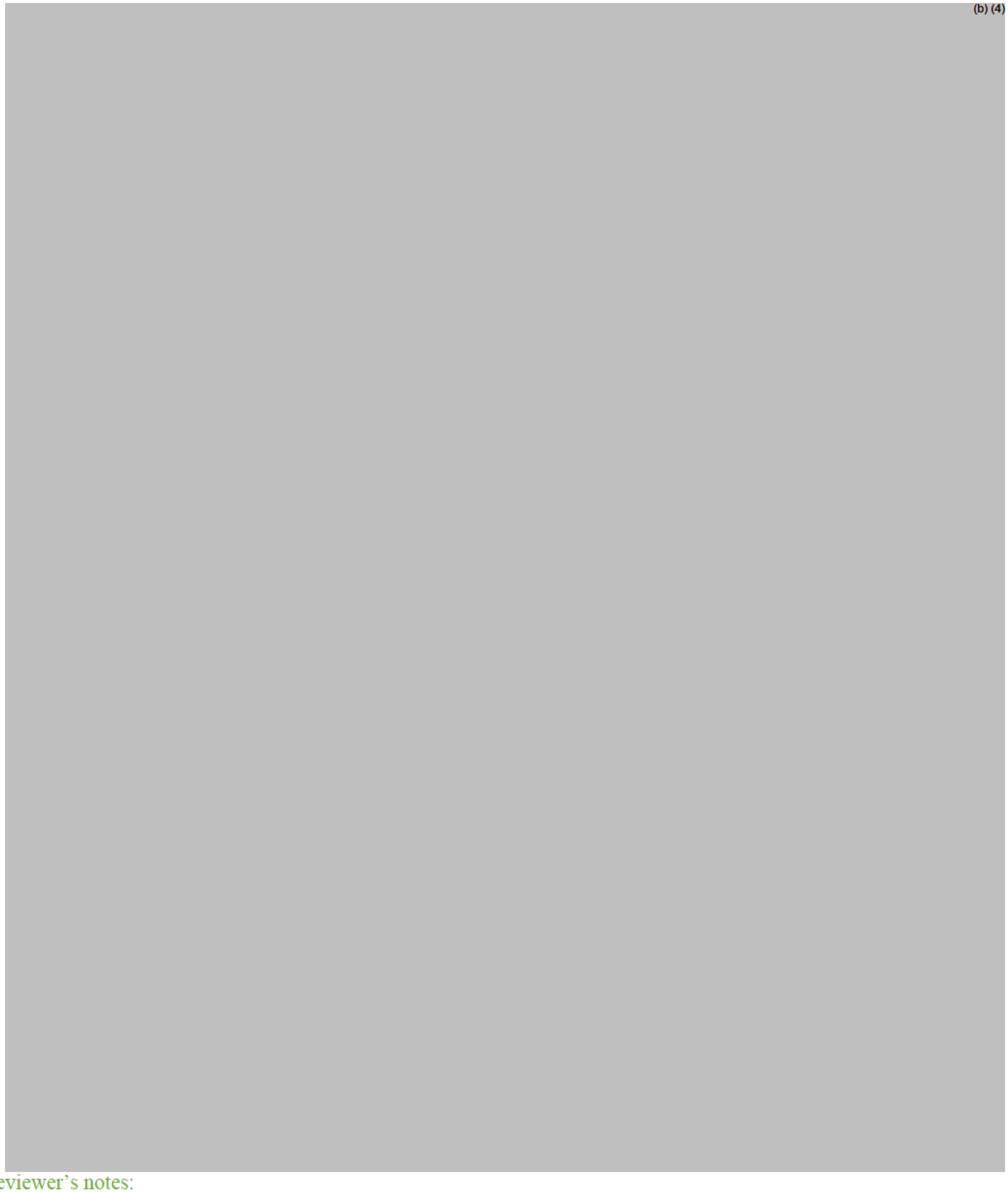


Reviewer's notes: The sponsor has summarized the SOPs that include compliance to relevant elements of 21 CFR 820 subpart I. The summary provided above indicates that the sponsor verifies the quality systems of the vendors through quality system agreements and quality assurance agreements which is often acceptable for combination product device manufacturers. The definition of deviations provided above is acceptable and the use of a QMS system to document the evaluation of non-conformance is acceptable. The sponsor also indicates that the SOP specifies requirements of initial actions to be taken, including segregation of product. This is acceptable.

The sponsor's corrective and preventive action (CAPA) program includes a SOP which describes the procedures for implementation of CAPA actions and includes effectiveness check to confirm the effectiveness of the actions with respect to adverse events. This is acceptable.

The summary of batch disposition SOPs indicates that the sponsor has dedicated checklists and forms to perform the batch disposition review and dispose of non-conforming materials. This is acceptable.

(b) (4)



Reviewer's notes:

The sponsor's response outlines the procedures and controls in place to meet the relevant elements prescribed in CFR 820.120 Subpart K. The summary of the procedures and controls above are in line with the requirements of CFR 21 820.120 subpart K. the response is acceptable.

3. (b) (4)

(b) (4)

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(b) (4)

Reviewer's notes: The sponsor's response summarizes the elements of their CAPA SOPs that address the requested information. The provided summary of each element is acceptable.

4. (b) (4)

Reviewer's notes:

The sponsor's rationale for exclusion of the audible/visual feedback from the EPRs is acceptable. The provided test results during design verification of the device is acceptable in providing verification of the audible/visual device performance attribute. The response is acceptable.

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

Ionis Pharmaceuticals, Inc is requesting approval of Olezarsen . The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Ionis Pharmaceuticals, Inc. submitted this New NDA and requested Priority Review (this request has been granted). The drug product (Olezarsen) has been granted Orphan Drug Designation. In the meantime, the CMC team is requesting a device engineering review consult.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device description, device design verification, device performance data and release and stability data.

This review will not cover the following review areas:

This Priority review will focus on the review of device engineering performance data. Per the requester, this review will focus on : 1. Device design verification - if the engineering design is adequate or not 2. Device performance data review 3. Evaluation of device performance specification at release and stability -acceptable or not

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

There are no prior interaction or related files.

3.3. Indications for Use

Combination Product	Indications for Use
Olezarsen	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS).
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.P.1
0001	3.2.P.5 (5.1-5.6)
0001	3.2.P.5.2.2.13
0001	3.2.P.5.3.7
0001	3.2.P.3.5
0001	3.2.R

4. DEVICE DESCRIPTION

4.1. Device Description

Olezarsen Solution for Injection is a sterile, single-dose, ready-to-use parenteral solution of olezarsen intended for monthly subcutaneous (SC) administration. The formulation contains 100 mg/mL olezarsen free acid (105 mg/mL olezarsen sodium) (b) (4), at a target pH 7.4. Sodium chloride is added to (b) (4) (b) (4). The solution appears clear and colorless to yellow. The drug product is packaged with 0.8 mL deliverable volume in a 1 mL Long (1mL L) staked needle glass prefilled syringe (PFS) closed with a (b) (4) rubber plunger stopper. The PFS is assembled into an autoinjector for the final drug product presentation. The autoinjector delivers a single dose of 80 mg Olezarsen.

The autoinjector is a prefilled, single-dose, disposable device intended for subcutaneous injection of olezarsen. The applicant has developed the olezarsen autoinjector based on (b) (4) platform autoinjector called (b) (4). The autoinjector carries the placeholder name "TRADENAME" for testing purposes

The olezarsen autoinjector consists of the following components:

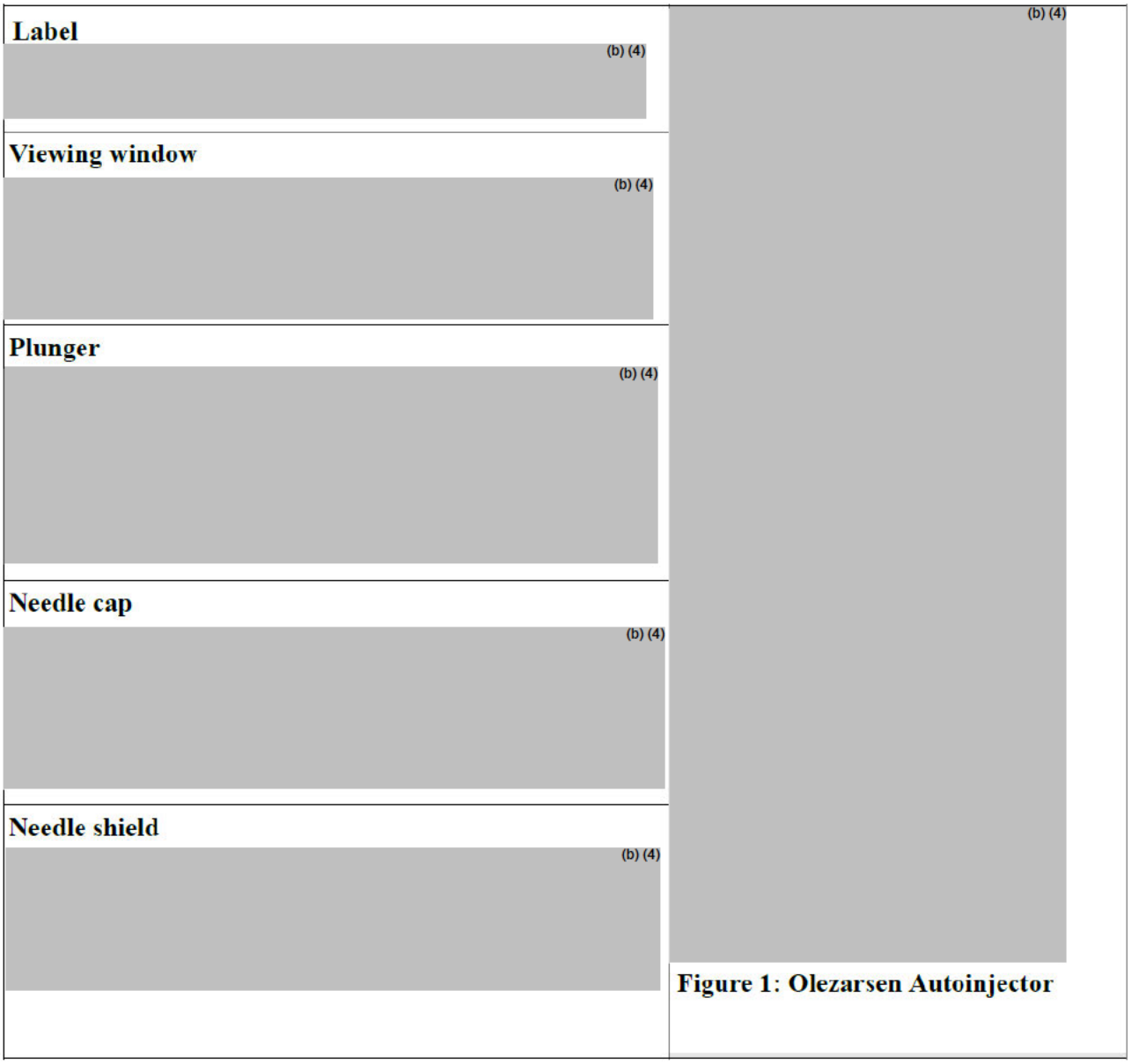
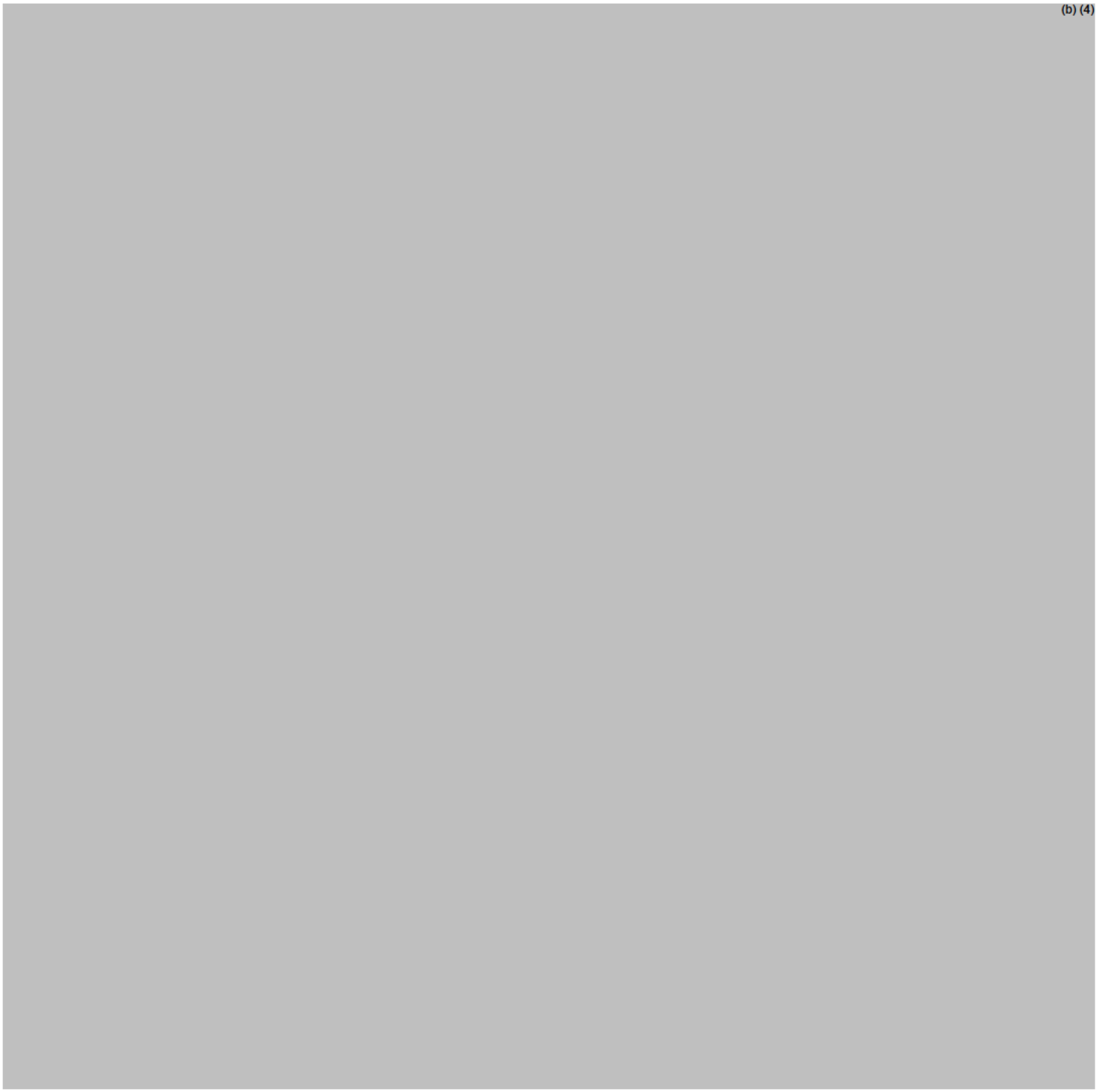


Figure 1: Olezarsen Autoinjector

The olezarsen autoinjector comprises (b) (4)
).
The olezarsen autoinjector is labeled and packaged in an opaque carton with a partition to secure the autoinjector and protect from light. Package inserts are placed on top of the autoinjector, and the carton is sealed. (b) (4)
(b) (4) are placed on the carton.

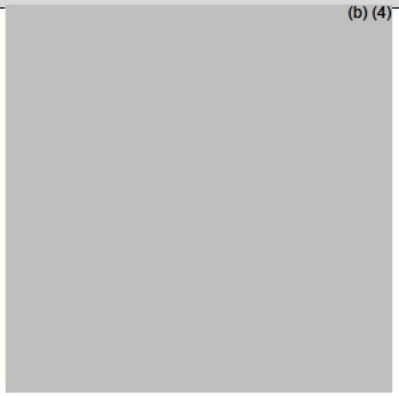
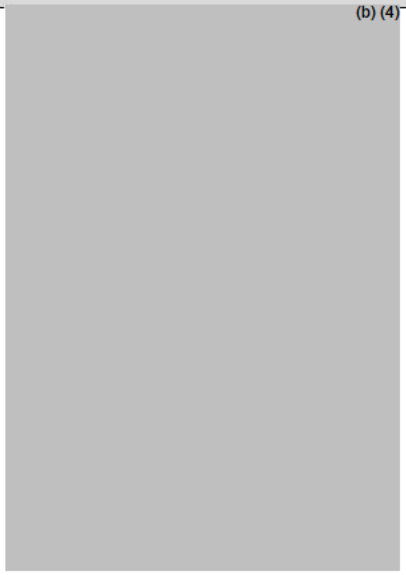
Table 4: Autoinjector Subassembly Unit

(b) (4)



4.2. Steps for Using the Device

Table 2: IFU workflow

Step	IFU excerpt
Storage	
Store the autoinjector in its carton in the refrigerator (or at room temperature for up to 6 weeks)	(b) (4) 
Prepare for injection	
Retrieve the autoinjector from the refrigerator Let the autoinjector come to room temperature for 30 minutes Remove the autoinjector from the carton	(b) (4) 

Step	IFU excerpt
Check the expiration date Inspect the drug product through the autoinjector medication window	(b) (4)
Select injection site	

Step	IFU excerpt
Wash hands Clean injection site	(b) (4)
Inject	
Remove needle cap Dispose of needle cap	(b) (4)

Step	IFU excerpt
Position autoinjector with orange needle shield end toward skin at a 90° angle Inject by pressing the orange tip (needle shield) of the autoinjector all the way against the skin Administer dose by holding autoinjector pressed against skin	(b) (4)
Check that the injection is complete Lift autoinjector from skin	
After injection	

Step	IFU excerpt
Dispose of the used autoinjector in a sharps container	(b) (4) [redacted]

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description provides an overview of the device function and design. The steps for using the device are clear and seem to provide adequate information to understand the device design and function. There are no deficiencies regarding the device description from the device perspective.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		
Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications	x		
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors			Deferred
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

Reviewer Comments
The device constituent labeling is adequate.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device constituent labeling is adequate. Therefore, no deficiencies were issued. Final review of the labeling is deferred to CDER and DMEPA.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial			x

Bioequivalence Study utilized to-be-marketed device			x
Verification methods relevant to specific use conditions as described in design documents and labeling			x
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)			x
Traceability demonstrated for specifications to performance data	x		

Reviewer Comments

The sponsor has provided summary information on the risk evaluation, traceability analysis documentation in module 3.2.R Regional Information section. The details of the risk evaluation and traceability analysis is not provided for review. This is a deficiency.

Updated 09/27/2024: The sponsor has provided adequate response to the issued IR#1. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor's response provides summary details of the risk evaluation, hazards evaluation and mitigation controls. The sponsor's response is acceptable.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Activation Force	(b) (4) N
Injection Time	NMT (b) (4) seconds
Delivered Volume	NLT (b) (4) mL
Cap Removal Force	(b) (4) N
Needle Extension	(b) (4) mm
Needle Cover Lockout Displacement	(b) (4) mm

Reviewer Comments

The sponsor has identified appropriate design input and output requirements for the Auto-injector device constituent. The specified acceptance criteria are acceptable for the identified design inputs and are in line with commonly accepted specifications for the device type. However, the sponsor has not included audible/visual feedback as a part of their EPRs. There is not provided rationale for excluding visual and audible feedback from device performance EPRs. Therefore, the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for the exclusion of audible/visual feedback from the device EPRs. Please see deficiency above.

Update 09/30/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable rationale for exclusion of the audible/visual feedback from the EPRs and has provided summary of acceptable test results for the design verification of the audible/visual feedback device performance attribute.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA

Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-Based Injection Systems	**Y**	**Y**
ISO 11608-5:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions	**Y**	**Y**
ISO 23908:2011: Sharps Injury Protection – Requirements and Test Methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	**Y**	**Y**
ISO 11040-4:2015: Prefilled syringes – Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling	**Y**	**Y**
ISO 11040-5:2012: Prefilled syringes – Part 5: Plunger stoppers for injectables	**Y**	**Y**
ISO 9626:2016: Stainless steel tubing for the manufacture of medical devices – Requirements and test methods	**Y**	**Y**
ASTM D4169-22: Standard Practice for Performance Testing of Shipping Containers and Systems	**Y**	**Y**
ASTM F1980-21: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	**Y**	**Y**
ISO 10993-1:2018: Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process	**Y**	**Y**
ISO 14971:2019: Medical Devices – Application of Risk Management to Medical Devices	**Y**	**Y**

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments

The sponsor has indicated conformance with the applicable Medical Device Guidance and performance standards documents. The provided list of standards and guidance documents is acceptable. The acceptability of the performed verification testing is reviewed in the below section. There are no deficiencies regarding the applicable standards and guidance documents with which the sponsor is expected to conform. However, the sponsor has not included audible/visual feedback as part of the device EPRs. There is no rationale provided for this exclusion. Therefore, the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for their exclusion from EPRs.

Update 09/30/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable rationale for exclusion of the audible/visual feedback from the EPRs and has provided summary of acceptable test results for the design verification of the audible/visual feedback device performance attribute.

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

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8.2. Hazard Analysis and Risk Summary Report

Reviewer Comments
While the sponsor has provided a summary of risk management activities and hazard analysis procedures, the details of the risk analysis and hazard analysis documents such as a breakdown of identified hazards, identified mitigations/controls and verification of risk activities is not provided. This deficiency is communicated via IR. Updated 09/27/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable risk management plan, hazard analysis, and risk management report.

Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor is requested to provide detailed description of risk analysis and hazard analysis documents, including identification of the risks and hazards associated with the device per the sponsor's benefit-risk analysis.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap Removal Force	(b) (4)	Y, conforms with ISO 11608-1:2022	Y	Y	Y
Activation Force		Y, conforms with ISO 11608-5:2022	Y	Y	Y

Delivered Volume	(b) (4)	Y, conforms with ISO 11608-5:2022	Y	Y	Y
Injection Time		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Needle Extension		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Needle Cover Lockout Displacement		Y, conforms with ISO 23908:2011	Y	Y	Y

9.1.1. Evaluation of Test Methods

(b) (4)

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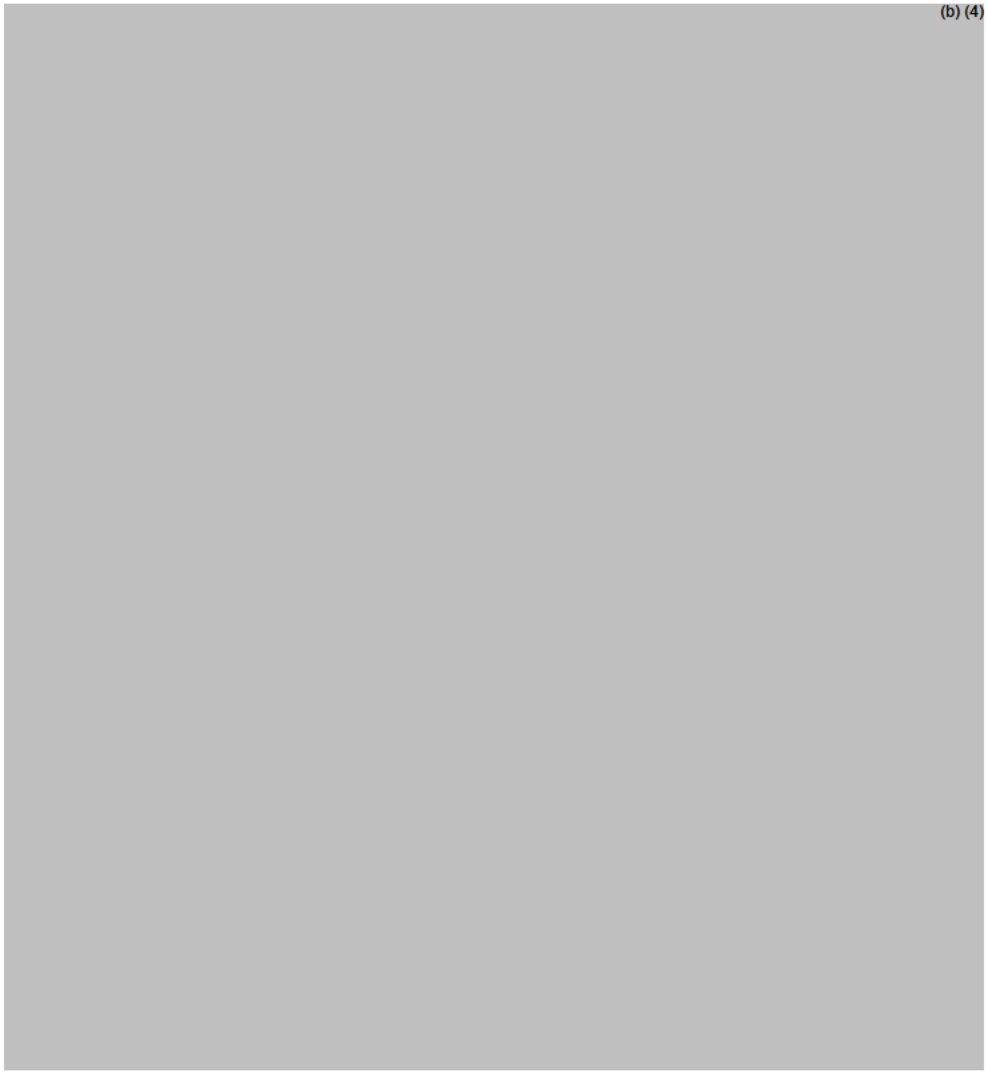

Reviewer Comment

The sponsor has provided test results for the device performance requirements based on the acceptance criteria and test methods described in the applicable referenced standards. The sponsor has also performed verification testing following system lifecycle preconditioning, including transit testing per ASTM D4169. The results show that the device continues to perform per the identified specification acceptance criteria after transit testing with a confidence and reliability of (b) (4)%.

Accelerated aging was defined in accordance with ASTM F 1980. The autoinjector sub-assembly units were aged to (b) (4) years and the finished autoinjector assembly was aged to (b) (4) years for a total of (b) (4) years of total real time aging. Fully assembled water filled autoinjectors were subject to (b) (4) years of accelerated aging at 55 ºC.

The (b) (4) year accelerated aging of water filled autoinjectors at 55 ºC is acceptable because the sponsor has also performed (b) (4) years of sub-assembly accelerated aging and (b) (4) years of finished autoinjector accelerated aging. Also, the sponsor commits to continue to perform real life aging of the final finished device to at least (b) (4) . Therefore, the provided device performance testing after accelerated aging is acceptable. The verification performance testing after accelerated aging meets the identified acceptance criteria with a (b) (4) % confidence / (b) (4) % reliability.

(b) (4)

(b) (4)

Reviewer Comment

The sponsor has performed adequate device stability testing at accelerated aging and long-term storage conditions. The shelf life of the combination product device is (b) (4) months from the time of manufacture. The sponsor commits to continue the stability study for at least (b) (4) months. The results indicate that the device subject device continues to perform per the device specification post storage conditions.

Design verification:

(b) (4)

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Reviewer Comment

The sponsor has performed adequate design verification testing of the Olezarsen Autoinjector 80 mg/0.8 ml configuration. The test acceptance criteria is consistent throughout the submission and the test results after preconditioning meet the performance specifications. Testing was conducted with (b) (4)% confidence and (b) (4)% reliability in results. The test results are acceptable.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has performed adequate verification and validation testing of the device constituent's Essential Performance Requirements (EPRs) per the recognized identified standards as listed above. The sponsor has performed device performance verification testing post accelerated aging and shipping pre-conditioning per the applicable referenced standards. The test results meet the performance acceptance criteria with (b)(4)% confidence / (b)(4)% reliability. Review of the device engineering performance validation/verification testing finds the sponsor's test methods and results acceptable. There are no performance deficiencies from the device perspective.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

10.FACILITIES & QUALITY SYSTEMS

10.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Reviewer Comments

A facilities inspection review has been previously completed. Please refer to the facilities inspection memo under ICCR#00988361.

Update 10/03/2024: In inspection of the final device manufacturing facility ([redacted](b)(4)) was completed from [redacted](b)(4) to [redacted](b)(4). Based on the Form FDA-483 shared with CDRH on 09/30/2024 and discussions with CDER and the inspector on 10/03/2024, the inspection did not identify any device related 483 observations, therefore, CDRH is recommending APPR.

10.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

10.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

[redacted](b)(4)

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(b) (4)

Reviewer Comments
The sponsor has provided adequate summary of the manufacturing processes for the combination product. The provided information regarding the assembly processes of the autoinjector seem acceptable. (b) (4) performs the autoinjector component manufacturing, but the final assembly is performed by Ionis Pharmaceuticals at their (b) (4) The provided information is acceptable.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

10.2.1. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

☐ Device QSR-based
☑ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)

		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s):	**Reviewer Discussion –** Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion –** Reviewed in Section 10.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion –** No Installation is required for this device.
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion –** No servicing is required for this device.
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion –** Reviewed in Section 10.3
Subpart H – Acceptance Activities	Firm(s):	(b) (4)

Subpart I – Nonconforming Product	Firm(s):	(b) (4)
Subpart K – Labeling and Packaging Controls	Firm(s):	

Reviewer Comments

The sponsor's provided information on the quality system sub-parts is not complete. The sponsor has not provided adequate description of how non-conforming products are handled during manufacturing and assembly of the combination product. The sponsor also has not provided adequate information on the measures taken to ensure the integrity of labeling and packaging of the products post manufacturing and storage. This is a deficiency.

Updated 09/27/2024: The sponsor's response to the issued IR provides a summary of procedures (SOPs) and controls that the sponsor uses to achieve a hybrid approach for the drug product's management controls to address relevant elements of 21 CFR 820, including subparts I and K, and ensure safety and effectiveness of the olezarsen autoinjector in administering the drug and preventing patient harm. The provided information indicates adequacy of the sponsor's SOPs and management controls. The response is acceptable. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

10.2.1. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)

(b) (4)

Reviewer Comments

The sponsor has not provided complete information regarding the CAPA investigation activities. The relevant elements do not appear to be included in the provided information. This is a deficiency.

Updated 09/27/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor's response summarizes the elements of the sponsor's CAPA procedures that satisfy the requested information.

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

10.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g., emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Cap Removal Force	(b) (4)	Y
Activation Force		Y

Delivered Volume	(b) (4)	Y
Injection Time		Y
Needle Extension		Y
Needle cover lockout displacement		Y

Reviewer Comments

The sponsor has listed the above EPRs and acceptance criteria for release testing of the final finished product.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

10.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has not provided comprehensive information regarding their CAPA procedures. This is a deficiency. Updated 09/27/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor's response summarizes the elements of the sponsor's CAPA procedures that satisfy the requested information.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

<<END OF REVIEW>>

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AKM KHAIRUZZAMAN
10/09/2024 01:37:04 PM
The Office of Pharmaceutical Quality Recommends an Approval for this NDA

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	9/30/2024		
To:	Oluwafunmike Ajomale FDA/OC/CDER/OPQ/OPRO/DRBPMIII/		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Farzaneh Akhavannik OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	Shruti Mistry, Injection Team OPEQ/OHT3/DHT3C		
Subject	Device engineering review consult for the new NDA 218614		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 9/12/2024 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 9/30/2024 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Farzaneh S. Akhavannik -S Digitally signed by Farzaneh S. Akhavannik -S Date: 2024.09.30 16:19:53 -04'00'	Shruti N. Mistry -S	2024.10.01 11:06:09 -04'00'

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 218614
Sponsor	Ionis Pharmaceuticals, Inc
Drug/Biologic	Olezarsen
Indications for Use	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS)
Device Constituent	Auto-Injector
Related Files	Facilities Review for NDA 218614 (ICCR#00988361)

Review Team		
Lead Device Reviewer	*Farzaneh Akhavannik*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			The firm has provided adequate description of the device constituent.
Labeling	x			The firm has provided adequate labeling information.
Design Controls	x			The firm has provided adequate design controls documents.
Risk Analysis	x			The firm has provided adequate risk analysis documents.
Design Verification	x			Design verification review is performed through performance verification and validation testing. The provided testing is acceptable.
Consultant Discipline Reviews			x	This priority review is limited to engineering performance of the device constituent. Therefore, no discipline specific consults are requested.
Clinical Validation			x	This priority review is limited to engineering performance of the device constituent. The clinical validation review is deferred to CDER.
Human Factors Validation			x	This priority review is limited to engineering performance of the device constituent. The human factors review is deferred to CDER.
Facilities & Quality Systems			x	A facilities review was previous performed. Please see the facilities review memo dated 07/25/2024 (ICCR00988361).

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

Comment #: I have reviewed the performance of the Device design verification, Device Performance Data and Device release and stability data as requested in the clarification of consult request email dated August 20, 2024, as this is an expedited engineering review. The provided information regarding the device EPRs and performance verification of the device EPRs post aging and handling is acceptable, however, I also reviewed the risk analysis and quality systems data and identified some deficiencies related to lack of complete information provided. Risk analysis is important so we can understand the risk of the product, device constituent, and how the sponsor has mitigated them. The cGMP data and CAPA investigation information is important in verifying the sponsor's procedures and controls to ensure the continued conformance of the device design and performance specifications with the applicable standards and is required per 21 CFR 820, subpart I, K and J. I contacted consult RPM regarding the issue of IR deficiencies to be communicated with the sponsor on September 11, 2024, at which time she contacted, the CMC team who stated there is not enough time in their review clock for IR deficiencies. Therefore, CR deficiencies were issued. However, the CDER review team

communicated the deficiencies as IR after CDRH mid-cycle review was completed. The following IR deficiencies were issued:

1. (b) (4)

Reviewer's notes:

The sponsor has provided the device system FMEA which identified hazards and provides mitigations/controls for the identified hazards and verification of risk controls to reduce the identified risks to health. System failure modes, along with their end effects, are evaluated for the olezarsen combination product and is documented in Attachment 1 of the System FMEA ((b) (4)). Risk Controls have been identified for all failure modes within this System FMEA in order to reduce the probability of occurrence as low as possible. All failure modes that can result in a hazardous situation are rolled-up to the Hazard Analysis in order to ensure the Hazard Analysis provides a complete list of hazards, hazardous situations, and sequence of events, and that the risk of those hazards is assessed and controlled. The provided FMEA outlines appropriate hazards and mitigations for the device type.

The sponsor also provided the USE FMEA for ISIS 678354 for the Olezarsen Autoinjectors. The user FMEA documents the use error analysis for the development of the autoinjector, which includes the identification of use errors, potential effects, and related hazards/hazardous situations. The table below shows a summary of the critical tasks from the task analysis:

(b) (4)

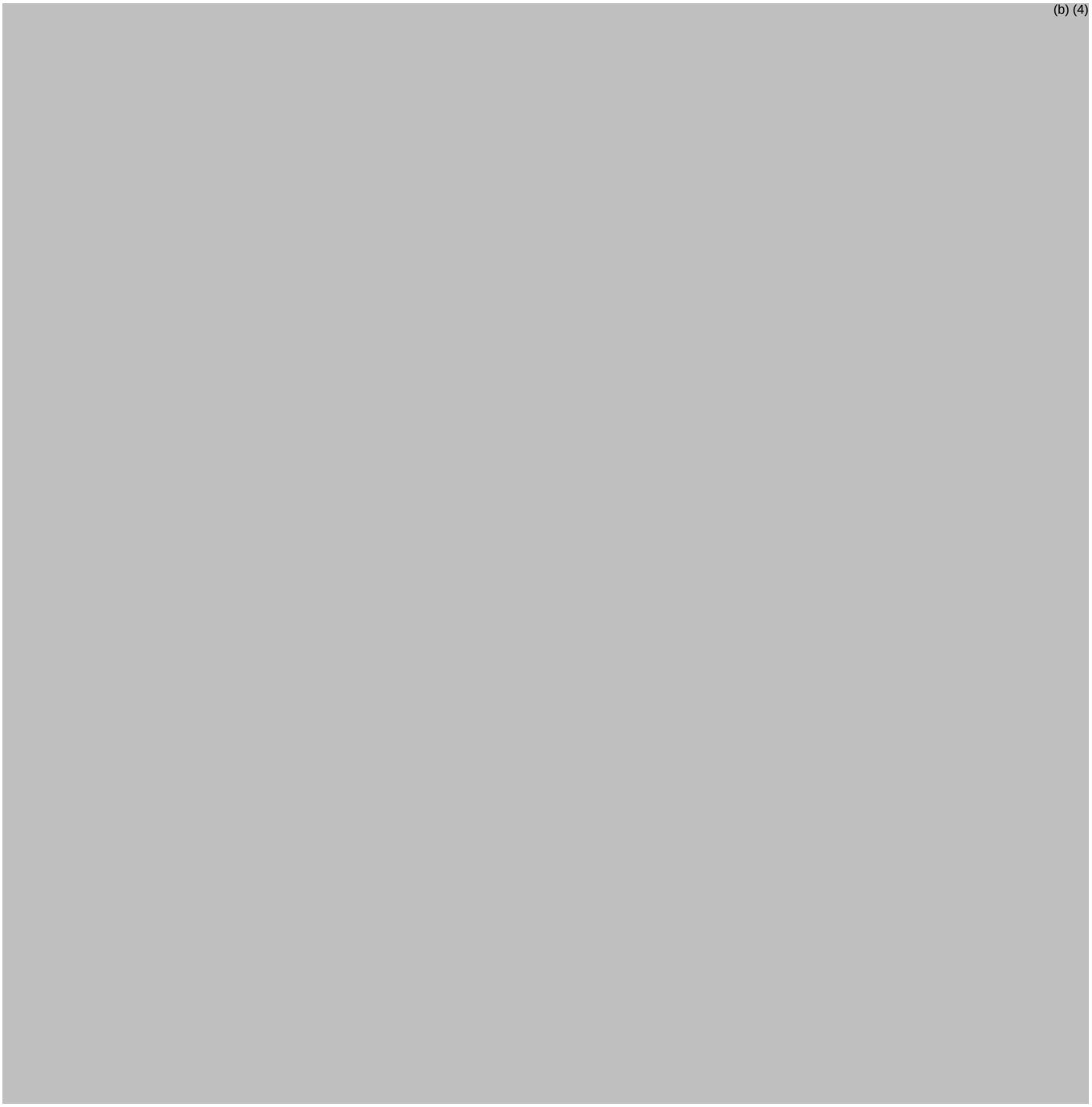
A Use FMEA table is also provided which adequately summarizes the analysis the use errors and potential foreseeable misuse along with their resultant effects. Please refer to Attachment 1 of document VV-QUAL-25847.

The third document provided is the Hazard analysis document for the autoinjector. The hazard analysis entails identifying hazards from possible occurrences or "hazardous effects". These hazardous events could stem from the environment or from human factors considerations during development of the olezarsen autoinjector, which included Risk Analysis, Risk Evaluation, and Risk Control. The hazard analysis is summarized in Attachment 1-Hazard analysis Table/Risk control Table (VV-QUAL-25621). The provided hazard analysis table adequately identified the potential hazards, their associated risk analysis, risk evaluation and risk control measures.

The individual risk controls are captured in the Risk Controls tab in Attachment 1, allowing reuse across multiple sequence of events. The Risk Controls tab identifies how each risk control has been implemented, the evidence of effectiveness of the risk control, and whether the risk control may result in a sequence of events associated with existing or new hazards or hazardous situations. Risk controls have been implemented in the form of design and labeling requirements, and affected sequence of events and Probability of sequence of events were evaluated and modified, if necessary, for the identified hazardous situations. The risk control table is complete and adequately describes reasonable controls for the identified hazards.

2. (b) (4)

(b) (4)

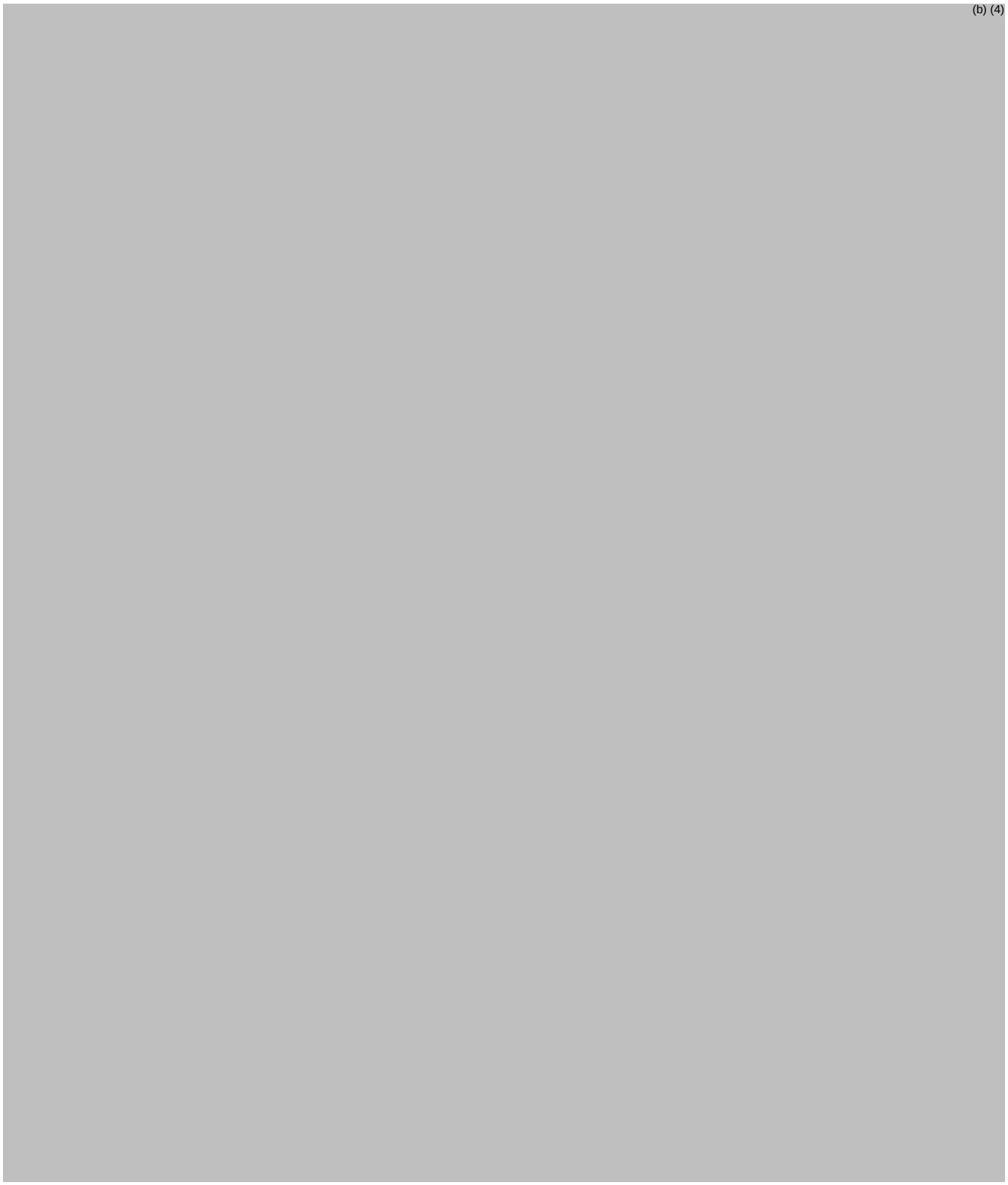


Reviewer's notes: The sponsor has summarized the SOPs that include compliance to relevant elements of 21 CFR 820 subpart I. The summary provided above indicates that the sponsor verifies the quality systems of the vendors through quality system agreements and quality assurance agreements which is often acceptable for combination product device manufacturers. The definition of deviations provided above is acceptable and the use of a QMS system to document the evaluation of non-conformance is acceptable. The sponsor also indicates that the SOP specifies requirements of initial actions to be taken, including segregation of product. This is acceptable.

The sponsor's corrective and preventive action (CAPA) program includes a SOP which describes the procedures for implementation of CAPA actions and includes effectiveness check to confirm the effectiveness of the actions with respect to adverse events. This is acceptable.

The summary of batch disposition SOPs indicates that the sponsor has dedicated checklists and forms to perform the batch disposition review and dispose of non-conforming materials. This is acceptable.

(b) (4)



Reviewer's notes:

The sponsor's response outlines the procedures and controls in place to meet the relevant elements prescribed in CFR 820.120 Subpart K. The summary of the procedures and controls above are in line with the requirements of CFR 21 820.120 subpart K. the response is acceptable.

3. (b) (4)

(b) (4)

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(b) (4)

Reviewer's notes: The sponsor's response summarizes the elements of their CAPA SOPs that address the requested information. The provided summary of each element is acceptable.

4. (b) (4)

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

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3. PURPOSE/BACKGROUND

3.1. Scope

Ionis Pharmaceuticals, Inc is requesting approval of Olezarsen . The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Ionis Pharmaceuticals, Inc. submitted this New NDA and requested Priority Review (this request has been granted). The drug product (Olezarsen) has been granted Orphan Drug Designation. In the meantime, the CMC team is requesting a device engineering review consult.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device description, device design verification, device performance data and release and stability data.

This review will not cover the following review areas:

This Priority review will focus on the review of device engineering performance data. Per the requester, this review will focus on : 1. Device design verification - if the engineering design is adequate or not 2. Device performance data review 3. Evaluation of device performance specification at release and stability -acceptable or not

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

There are no prior interaction or related files.

3.3. Indications for Use

Combination Product	Indications for Use
Olezarsen	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS).
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.P.1
0001	3.2.P.5 (5.1-5.6)
0001	3.2.P.5.2.2.13
0001	3.2.P.5.3.7
0001	3.2.P.3.5
0001	3.2.R

4. DEVICE DESCRIPTION

4.1. Device Description

Olezarsen Solution for Injection is a sterile, single-dose, ready-to-use parenteral solution of olezarsen intended for monthly subcutaneous (SC) administration. The formulation contains 100 mg/mL olezarsen free acid (105 mg/mL olezarsen sodium) (b) (4), at a target pH 7.4. Sodium chloride is added to (b) (4) (b) (4). The solution appears clear and colorless to yellow. The drug product is packaged with 0.8 mL deliverable volume in a 1 mL Long (1mL L) staked needle glass prefilled syringe (PFS) closed with a (b) (4) rubber plunger stopper. The PFS is assembled into an autoinjector for the final drug product presentation. The autoinjector delivers a single dose of 80 mg Olezarsen.

The autoinjector is a prefilled, single-dose, disposable device intended for subcutaneous injection of olezarsen. The applicant has developed the olezarsen autoinjector based on (b) (4) platform autoinjector called (b) (4). The autoinjector carries the placeholder name "TRADENAME" for testing purposes

The olezarsen autoinjector consists of the following components:

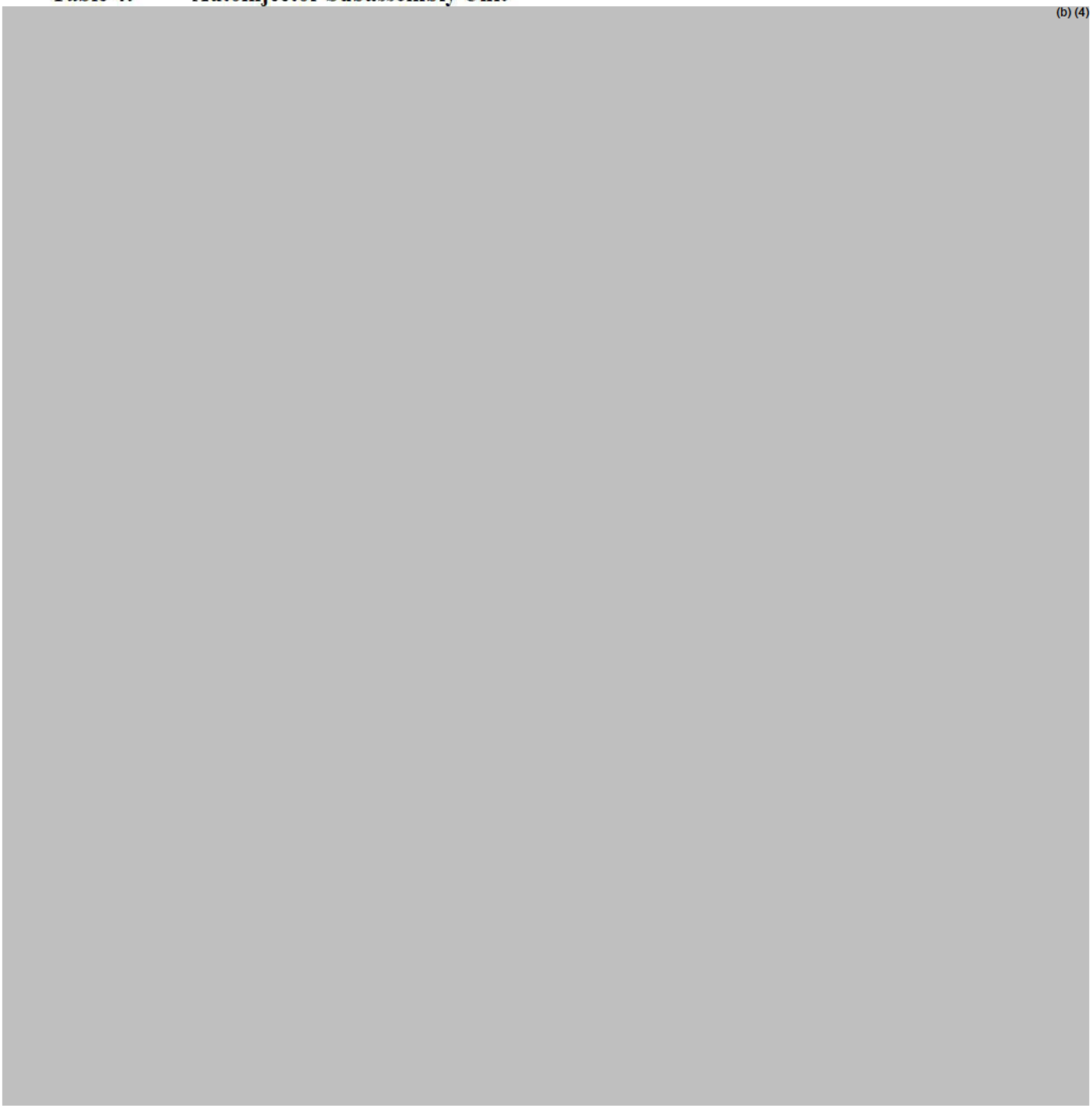
Figure 1: Olezarsen Autoinjector

The olezarsen autoinjector comprises (b) (4)

The olezarsen autoinjector is labeled and packaged in an opaque carton with a partition to secure the autoinjector and protect from light. Package inserts are placed on top of the autoinjector, and the carton is sealed. (b) (4) (b) (4) are placed on the carton.

Table 4: Autoinjector Subassembly Unit

(b) (4)



4.2. Steps for Using the Device

Table 2: IFU workflow

Step	IFU excerpt
Storage	
Store the autoinjector in its carton in the refrigerator (or at room temperature for up to 6 weeks)	(b) (4)
Prepare for injection	
Retrieve the autoinjector from the refrigerator Let the autoinjector come to room temperature for 30 minutes Remove the autoinjector from the carton	(b) (4)

Step	IFU excerpt
Check the expiration date Inspect the drug product through the autoinjector medication window	(b) (4)
Select injection site	

Step	IFU excerpt
Wash hands Clean injection site	(b) (4)
Inject	
Remove needle cap Dispose of needle cap	(b) (4)

Step	IFU excerpt
Position autoinjector with orange needle shield end toward skin at a 90° angle Inject by pressing the orange tip (needle shield) of the autoinjector all the way against the skin Administer dose by holding autoinjector pressed against skin	(b) (4)
Check that the injection is complete Lift autoinjector from skin	
After injection	

Step	IFU excerpt
Dispose of the used autoinjector in a sharps container	(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description provides an overview of the device function and design. The steps for using the device are clear and seem to provide adequate information to understand the device design and function. There are no deficiencies regarding the device description from the device perspective.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		
Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications	x		
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors			Deferred
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

Reviewer Comments
The device constituent labeling is adequate.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device constituent labeling is adequate. Therefore, no deficiencies were issued. Final review of the labeling is deferred to CDER and DMEPA.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial			x

Bioequivalence Study utilized to-be-marketed device			x
Verification methods relevant to specific use conditions as described in design documents and labeling			x
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)			x
Traceability demonstrated for specifications to performance data	x		

Reviewer Comments

The sponsor has provided summary information on the risk evaluation, traceability analysis documentation in module 3.2.R Regional Information section. The details of the risk evaluation and traceability analysis is not provided for review. This is a deficiency.

Updated 09/27/2024: The sponsor has provided adequate response to the issued IR#1. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor's response provides summary details of the risk evaluation, hazards evaluation and mitigation controls. The sponsor's response is acceptable.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Activation Force	(b) (4) N
Injection Time	NMT (b) (4) seconds
Delivered Volume	NLT (b) (4) mL
Cap Removal Force	(b) (4) N
Needle Extension	(b) (4) mm
Needle Cover Lockout Displacement	(b) (4) mm

Reviewer Comments

The sponsor has identified appropriate design input and output requirements for the Auto-injector device constituent. The specified acceptance criteria are acceptable for the identified design inputs and are in line with commonly accepted specifications for the device type. However, the sponsor has not included audible/visual feedback as a part of their EPRs. There is not provided rationale for excluding visual and audible feedback from device performance EPRs. Therefore, the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for the exclusion of audible/visual feedback from the device EPRs. Please see deficiency above.

Update 09/30/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable rationale for exclusion of the audible/visual feedback from the EPRs and has provided summary of acceptable test results for the design verification of the audible/visual feedback device performance attribute.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA

Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-Based Injection Systems	**Y**	**Y**
ISO 11608-5:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions	**Y**	**Y**
ISO 23908:2011: Sharps Injury Protection – Requirements and Test Methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	**Y**	**Y**
ISO 11040-4:2015: Prefilled syringes – Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling	**Y**	**Y**
ISO 11040-5:2012: Prefilled syringes – Part 5: Plunger stoppers for injectables	**Y**	**Y**
ISO 9626:2016: Stainless steel tubing for the manufacture of medical devices – Requirements and test methods	**Y**	**Y**
ASTM D4169-22: Standard Practice for Performance Testing of Shipping Containers and Systems	**Y**	**Y**
ASTM F1980-21: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	**Y**	**Y**
ISO 10993-1:2018: Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process	**Y**	**Y**
ISO 14971:2019: Medical Devices – Application of Risk Management to Medical Devices	**Y**	**Y**

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments

The sponsor has indicated conformance with the applicable Medical Device Guidance and performance standards documents. The provided list of standards and guidance documents is acceptable. The acceptability of the performed verification testing is reviewed in the below section. There are no deficiencies regarding the applicable standards and guidance documents with which the sponsor is expected to conform. However, the sponsor has not included audible/visual feedback as part of the device EPRs. There is no rationale provided for this exclusion. Therefore, the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for their exclusion from EPRs.

Update 09/30/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable rationale for exclusion of the audible/visual feedback from the EPRs and has provided summary of acceptable test results for the design verification of the audible/visual feedback device performance attribute.

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

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8.2. Hazard Analysis and Risk Summary Report

Reviewer Comments
While the sponsor has provided a summary of risk management activities and hazard analysis procedures, the details of the risk analysis and hazard analysis documents such as a breakdown of identified hazards, identified mitigations/controls and verification of risk activities is not provided. This deficiency is communicated via IR. Updated 09/27/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor has provided acceptable risk management plan, hazard analysis, and risk management report.

Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor is requested to provide detailed description of risk analysis and hazard analysis documents, including identification of the risks and hazards associated with the device per the sponsor's benefit-risk analysis.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap Removal Force	(b) (4)	Y, conforms with ISO 11608-1:2022	Y	Y	Y
Activation Force		Y, conforms with ISO 11608-5:2022	Y	Y	Y

Delivered Volume	(b) (4)	Y, conforms with ISO 11608-5:2022	Y	Y	Y
Injection Time		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Needle Extension		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Needle Cover Lockout Displacement		Y, conforms with ISO 23908:2011	Y	Y	Y

9.1.1. Evaluation of Test Methods

(b) (4)

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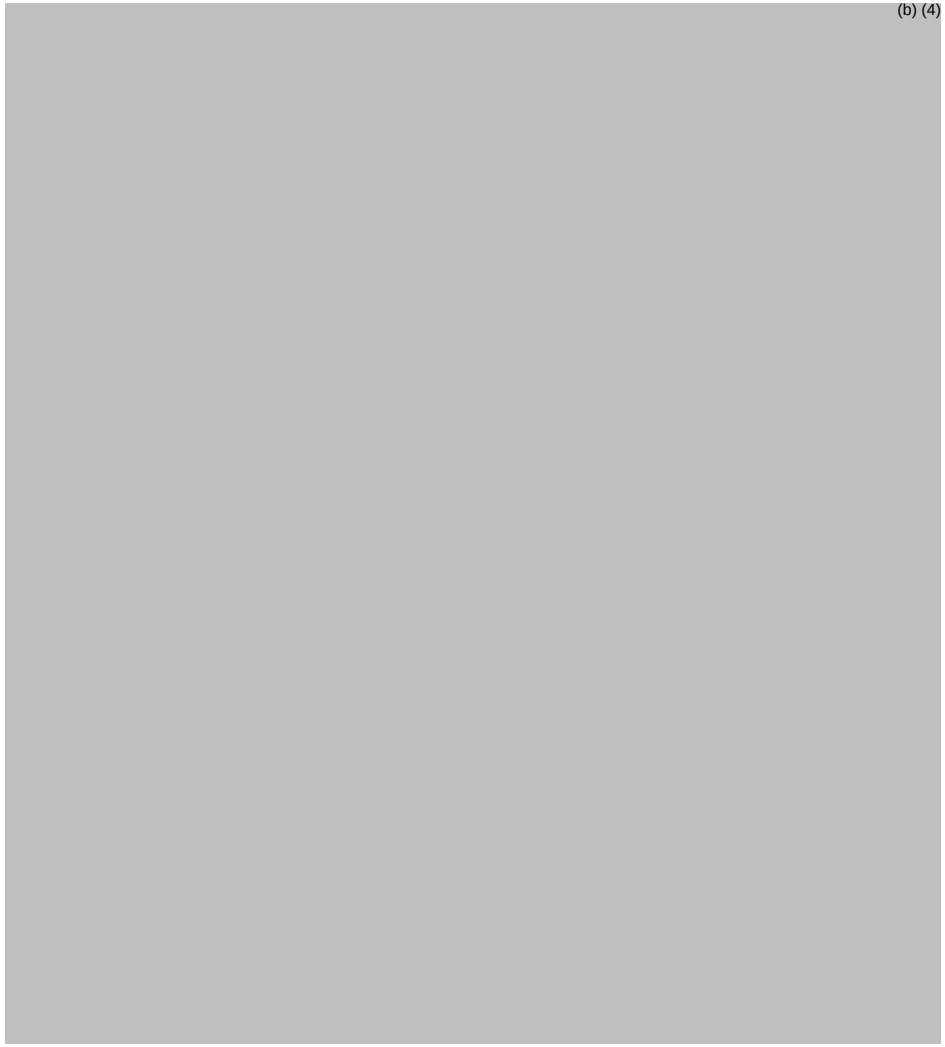

Reviewer Comment

The sponsor has provided test results for the device performance requirements based on the acceptance criteria and test methods described in the applicable referenced standards. The sponsor has also performed verification testing following system lifecycle preconditioning, including transit testing per ASTM D4169. The results show that the device continues to perform per the identified specification acceptance criteria after transit testing with a confidence and reliability of (b) (4)%.

Accelerated aging was defined in accordance with ASTM F 1980. The autoinjector sub-assembly units were aged to (b) (4) years and the finished autoinjector assembly was aged to (b) (4) years for a total of (b) (4) years of total real time aging. Fully assembled water filled autoinjectors were subject to (b) (4) years of accelerated aging at 55 ºC.

The (b) (4) year accelerated aging of water filled autoinjectors at 55 ºC is acceptable because the sponsor has also performed (b) (4) years of sub-assembly accelerated aging and (b) (4) years of finished autoinjector accelerated aging. Also, the sponsor commits to continue to perform real life aging of the final finished device to at least (b) (4) (b) (4). Therefore, the provided device performance testing after accelerated aging is acceptable. The verification performance testing after accelerated aging meets the identified acceptance criteria with a (b) (4)% confidence / (b) (4)% reliability.

(b) (4)

(b) (4)

Reviewer Comment

The sponsor has performed adequate device stability testing at accelerated aging and long-term storage conditions. The shelf life of the combination product device is (b) (4) months from the time of manufacture. The sponsor commits to continue the stability study for at least (b) (4) months. The results indicate that the device subject device continues to perform per the device specification post storage conditions.

Design verification:

(b) (4)

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Reviewer Comment

The sponsor has performed adequate design verification testing of the Olezarsen Autoinjector 80 mg/0.8 ml configuration. The test acceptance criteria is consistent throughout the submission and the test results after preconditioning meet the performance specifications. Testing was conducted with (b) (4)% confidence and (b) (4)% reliability in results. The test results are acceptable.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has performed adequate verification and validation testing of the device constituent's Essential Performance Requirements (EPRs) per the recognized identified standards as listed above. The sponsor has performed device performance verification testing post accelerated aging and shipping pre-conditioning per the applicable referenced standards. The test results meet the performance acceptance criteria with (b)(4)% confidence / (b)(4)% reliability. Review of the device engineering performance validation/verification testing finds the sponsor's test methods and results acceptable. There are no performance deficiencies from the device perspective.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

10.FACILITIES & QUALITY SYSTEMS

10.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Reviewer Comments
A facilities inspection review has been previously completed. Please refer to the facilities inspection memo under ICCR#00988361

10.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

10.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)

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(b) (4)

Reviewer Comments

The sponsor has provided adequate summary of the manufacturing processes for the combination product. The provided information regarding the assembly processes of the autoinjector seem acceptable. (b) (4) performs the autoinjector component manufacturing, but the final assembly is performed by Ionis Pharmaceuticals at their (b) (4) . The provided information is acceptable.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

10.2.1. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
- ☐ Device QSR-based
- ☑ Drug cGMP-Based Streamline –
- ☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)

		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s):	**Reviewer Discussion** – Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion** – Reviewed in Section 10.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion** – No Installation is required for this device.
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion** – No servicing is required for this device.
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion** – Reviewed in Section 10.3
Subpart H – Acceptance Activities	Firm(s):	(b) (4)

Subpart I – Nonconforming Product	Firm(s):	(b) (4)
Subpart K – Labeling and Packaging Controls	Firm(s):	

Reviewer Comments

The sponsor's provided information on the quality system sub-parts is not complete. The sponsor has not provided adequate description of how non-conforming products are handled during manufacturing and assembly of the combination product. The sponsor also has not provided adequate information on the measures taken to ensure the integrity of labeling and packaging of the products post manufacturing and storage. This is a deficiency.

Updated 09/27/2024: The sponsor's response to the issued IR provides a summary of procedures (SOPs) and controls that the sponsor uses to achieve a hybrid approach for the drug product's management controls to address relevant elements of 21 CFR 820, including subparts I and K, and ensure safety and effectiveness of the olezarsen autoinjector in administering the drug and preventing patient harm. The provided information indicates adequacy of the sponsor's SOPs and management controls. The response is acceptable. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

10.2.1. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)

(b) (4)

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

10.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g., emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Cap Removal Force	(b) (4)	Y
Activation Force		Y

Delivered Volume	(b) (4)	Y
Injection Time		Y
Needle Extension		Y
Needle cover lockout displacement		Y

Reviewer Comments

The sponsor has listed the above EPRs and acceptance criteria for release testing of the final finished product.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

10.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has not provided comprehensive information regarding their CAPA procedures. This is a deficiency. Updated 09/27/2024: The sponsor has provided adequate response to the issued IR. Please refer to the Executive Summary and Recommendation section for review of the sponsor's response. The sponsor's response summarizes the elements of the sponsor's CAPA procedures that satisfy the requested information.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

<<END OF REVIEW>>

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OLUWAFUNMIKE O AJOMALE
10/01/2024 12:03:19 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	9/13/2024		
To:	Oluwafunmike Ajomale FDA/OC/CDER/OPQ/OPRO/DRBPMIII/		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Farzaneh Akhavannik OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Injection Team OPEQ/OHT3/DHT3C		
Subject	Device engineering review consult for the new NDA 218614		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 9/12/2024 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☑ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Farzaneh S. Akhavannik -S Digitally signed by Farzaneh S. Akhavannik -S Date: 2024.09.13 17:05:08 -04'00'	Shruti N. Mistry -S 2024.09.13 17:14:11 -04'00'	

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 218614
Sponsor	Ionis Pharmaceuticals, Inc
Drug/Biologic	Olezarsen
Indications for Use	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS)
Device Constituent	Auto-Injector
Related Files	Facilities Review for NDA 218614 (ICCR#00988361)

Review Team		
Lead Device Reviewer	*Farzaneh Akhavannik*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			The firm has provided adequate description of the device constituent.
Labeling	x			The firm has provided adequate labeling information.
Design Controls	x			The firm has provided adequate design controls documents.
Risk Analysis	x			The firm has provided adequate risk analysis documents.
Design Verification	x			Design verification review is performed through performance verification and validation testing. The provided testing is acceptable.
Consultant Discipline Reviews			x	This priority review is limited to engineering performance of the device constituent. Therefore, no discipline specific consults are requested.
Clinical Validation			x	This priority review is limited to engineering performance of the device constituent. The clinical validation review is deferred to CDER.
Human Factors Validation			x	This priority review is limited to engineering performance of the device constituent. The human factors review is deferred to CDER.
Facilities & Quality Systems			x	A facilities review was previous performed. Please see the facilities review memo dated 07/25/2024 (ICCR00988361).

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #: I have reviewed the performance of the Device design verification, Device Performance Data and Device release and stability data as requested in the clarification of consult request email dated August 20, 2024, as this is an expedited engineering review. The provided information regarding the device EPRs and performance verification of the device EPRs post aging and handling is acceptable, however, I also reviewed the risk analysis and quality systems data and identified some deficiencies related to lack of complete information provided. Risk analysis is important so we can understand the risk of the product, device constituent, and how the sponsor has mitigated them. The cGMP data and CAPA investigation information is important in verifying the sponsor's procedures and controls to ensure the continued conformance of the device design and performance specifications with the applicable standards and is required per 21 CFR 820, subpart I, K and J. I contacted consult RPM regarding the issue of IR deficiencies to be communicated with the sponsor on September 11, 2024 at which time she contacted, the CMC team who stated there is not enough time in their review clock for IR deficiencies. Therefore, CR deficiencies are issued. Please see the identified deficiencies below.

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☑ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. (b) (4)
2.
3.

4. [redacted] (b) (4)

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

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3. PURPOSE/BACKGROUND

3.1. Scope

Ionis Pharmaceuticals, Inc is requesting approval of Olezarsen . The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Ionis Pharmaceuticals, Inc. submitted this New NDA and requested Priority Review (this request has been granted). The drug product (Olezarsen) has been granted Orphan Drug Designation. In the meantime, the CMC team is requesting a device engineering review consult.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device description, device design verification, device performance data and release and stability data.

This review will not cover the following review areas:

This Priority review will focus on the review of device engineering performance data. Per the requester, this review will focus on : 1. Device design verification - if the engineering design is adequate or not 2. Device performance data review 3. Evaluation of device performance specification at release and stability -acceptable or not

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

There are no prior interaction or related files.

3.3. Indications for Use

Combination Product	Indications for Use
Olezarsen	Olezarsen Solution for Injection is an antisense oligonucleotide for treatment of Familial Chylomicronemia Syndrome (FCS).
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.P.1
0001	3.2.P.5 (5.1-5.6)
0001	3.2.P.5.2.2.13
0001	3.2.P.5.3.7
0001	3.2.P.3.5
0001	3.2.R

4. DEVICE DESCRIPTION

4.1. Device Description

Olezarsen Solution for Injection is a sterile, single-dose, ready-to-use parenteral solution of olezarsen intended for monthly subcutaneous (SC) administration. The formulation contains 100 mg/mL olezarsen free acid (105 mg/mL olezarsen sodium) (b) (4), at a target pH 7.4. Sodium chloride is added to (b) (4) (b) (4). The solution appears clear and colorless to yellow. The drug product is packaged with 0.8 mL deliverable volume in a 1 mL Long (1mL L) staked needle glass prefilled syringe (PFS) closed with a (b) (4) rubber plunger stopper. The PFS is assembled into an autoinjector for the final drug product presentation. The autoinjector delivers a single dose of 80 mg Olezarsen.

The autoinjector is a prefilled, single-dose, disposable device intended for subcutaneous injection of olezarsen. The applicant has developed the olezarsen autoinjector based on (b) (4) platform autoinjector called (b) (4). The autoinjector carries the placeholder name "TRADENAME" for testing purposes

The olezarsen autoinjector consists of the following components:

Label (b) (4)	(b) (4)
Viewing window (b) (4)	
Plunger (b) (4)	
Needle cap (b) (4)	
Needle shield (b) (4)	

The olezarsen autoinjector comprises (b) (4)

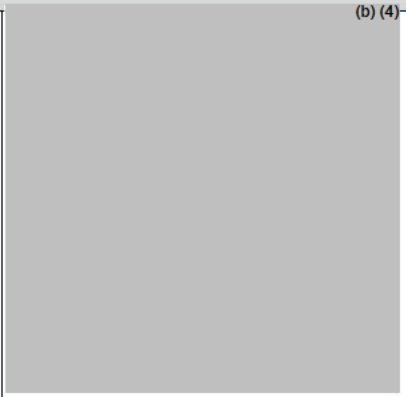
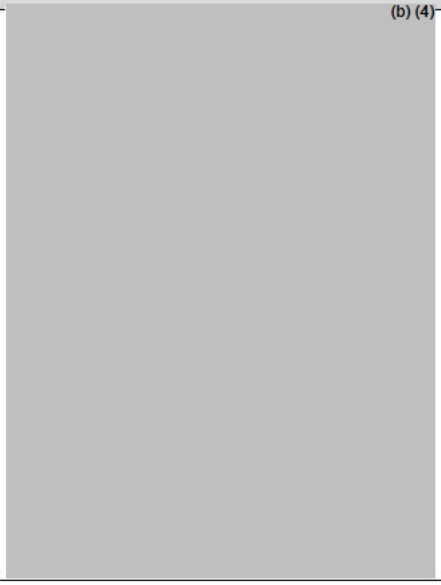
The olezarsen autoinjector is labeled and packaged in an opaque carton with a partition to secure the autoinjector and protect from light. Package inserts are placed on top of the autoinjector, and the carton is sealed. (b) (4) (b) (4) are placed on the carton.

Table 4: Autoinjector Subassembly Unit

(b) (4)

4.2. Steps for Using the Device

Table 2: IFU workflow

Step	IFU excerpt
Storage	
Store the autoinjector in its carton in the refrigerator (or at room temperature for up to 6 weeks)	(b) (4) 
Prepare for injection	
Retrieve the autoinjector from the refrigerator Let the autoinjector come to room temperature for 30 minutes Remove the autoinjector from the carton	(b) (4) 

Step	IFU excerpt
Check the expiration date Inspect the drug product through the autoinjector medication window	(b) (4)
Select injection site	

Step	IFU excerpt
Wash hands Clean injection site	(b) (4)
Inject	
Remove needle cap Dispose of needle cap	(b) (4)

Step	IFU excerpt
Position autoinjector with orange needle shield end toward skin at a 90° angle Inject by pressing the orange tip (needle shield) of the autoinjector all the way against the skin Administer dose by holding autoinjector pressed against skin	(b) (4)
Check that the injection is complete Lift autoinjector from skin	
After injection	

Step	IFU excerpt
Dispose of the used autoinjector in a sharps container	(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description provides an overview of the device function and design. The steps for using the device are clear and seem to provide adequate information to understand the device design and function. There are no deficiencies regarding the device description from the device perspective.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		
Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications	x		
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors			Deferred
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

Reviewer Comments
The device constituent labeling is adequate.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device constituent labeling is adequate. Therefore, no deficiencies were issued. Final review of the labeling is deferred to CDER and DMEPA.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)		x	
Mitigations are adequate to reduce risk to health		x	
Version history demonstrates risk management throughout design / development activities		x	
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial			x

Bioequivalence Study utilized to-be-marketed device			x
Verification methods relevant to specific use conditions as described in design documents and labeling			x
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)			x
Traceability demonstrated for specifications to performance data	x		

Reviewer Comments
The sponsor has provided summary information on the risk evaluation, traceability analysis documentation in module 3.2.R Regional Information section. The details of the risk evaluation and traceability analysis is not provided for review. This is a deficiency.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Activation Force	(b) (4) N
Injection Time	NMT (b) (4) seconds
Delivered Volume	NLT (b) (4) mL
Cap Removal Force	(b) (4) N
Needle Extension	(b) (4) mm
Needle Cover Lockout Displacement	(b) (4) mm

Reviewer Comments
The sponsor has identified appropriate design input and output requirements for the Auto-injector device constituent. The specified acceptance criteria are acceptable for the identified design inputs and are in line with commonly accepted specifications for the device type. However, the sponsor has not included audible/visual feedback as a part of their EPRs. There is not provided rationale for excluding visual and audible feedback from device performance EPRs. Therefore the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for the exclusion of audible/visual feedback from the device EPRs. Please see deficiency above.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y

Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-Based Injection Systems	Y	Y
ISO 11608-5:2022: Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions	Y	Y
ISO 23908:2011: Sharps Injury Protection – Requirements and Test Methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	Y	Y
ISO 11040-4:2015: Prefilled syringes – Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling	Y	Y
ISO 11040-5:2012: Prefilled syringes – Part 5: Plunger stoppers for injectables	Y	Y
ISO 9626:2016: Stainless steel tubing for the manufacture of medical devices – Requirements and test methods	Y	Y
ASTM D4169-22: Standard Practice for Performance Testing of Shipping Containers and Systems	Y	Y
ASTM F1980-21: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	Y	Y
ISO 10993-1:2018: Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process	Y	Y
ISO 14971:2019: Medical Devices – Application of Risk Management to Medical Devices	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A
Reviewer Comments The sponsor has indicated conformance with the applicable Medical Device Guidance and performance standards documents. The provided list of standards and guidance documents is acceptable. The acceptability of the performed verification testing is reviewed in the below section. There are no deficiencies regarding the applicable standards and guidance documents with which the sponsor is expected to conform. However, the sponsor has not included audible/visual feedback as part of the device EPRs. There is no rationale provided for this exclusion. Therefore, the sponsor is requested to include audible/visual feedback as part of the device EPRs or provide rationale for their exclusion from EPRs.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

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8.2. Hazard Analysis and Risk Summary Report

Reviewer Comments
While the sponsor has provided a summary of risk management activities and hazard analysis procedures, the details of the risk analysis and hazard analysis documents such as a breakdown of identified hazards, identified mitigations/controls and verification of risk activities is not provided. This is a deficiency.

Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A
Reviewer Comments The sponsor is requested to provide detailed description of risk analysis and hazard analysis documents, including identification of the risks and hazards associated with the device per the sponsor's benefit-risk analysis.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap Removal Force	(b) (4)	Y, conforms with ISO 11608-1:2022	Y	Y	Y
Activation Force		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Delivered Volume		Y, conforms with ISO 11608-5:2022	Y	Y	Y
Injection Time		Y, conforms with ISO 11608-5:2022	Y	Y	Y

Needle Extension	(b) (4)	Y, conforms with ISO 11608-5:2022	Y	Y	Y
Needle Cover Lockout Displacement		Y, conforms with ISO 23908:2011	Y	Y	Y

9.1.1. Evaluation of Test Methods

(b) (4)

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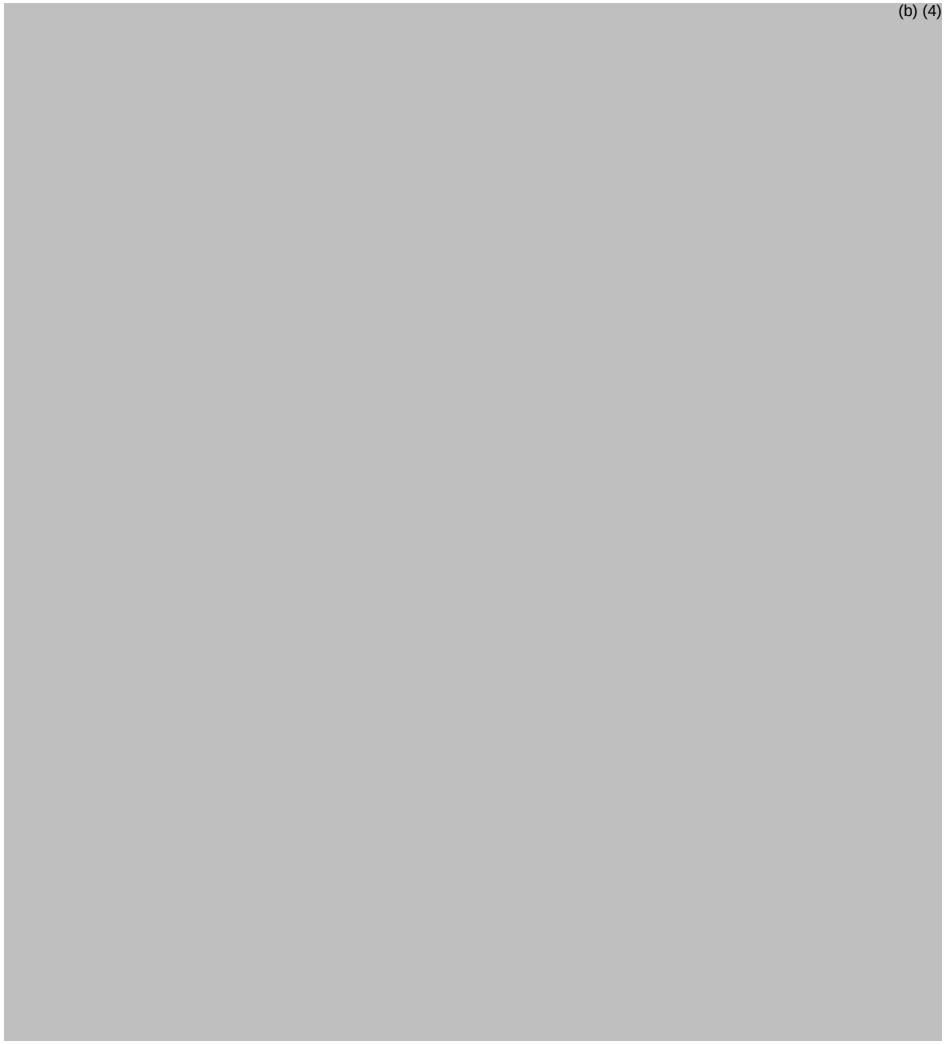

Reviewer Comment

The sponsor has provided test results for the device performance requirements based on the acceptance criteria and test methods described in the applicable referenced standards. The sponsor has also performed verification testing following system lifecycle preconditioning, including transit testing per ASTM D4169. The results show that the device continues to perform per the identified specification acceptance criteria after transit testing with a confidence and reliability of (b) (4) %.

Accelerated aging was defined in accordance with ASTM F 1980. The autoinjector sub-assembly units were aged to (b) (4) years and the finished autoinjector assembly was aged to (b) (4) years for a total of (b) (4) years of total real time aging. Fully assembled water filled autoinjectors were subject to (b) (4) years of accelerated aging at 55 ºC.

The (b) (4) year accelerated aging of water filled autoinjectors at 55 ºC is acceptable because the sponsor has also performed (b) (4) years of sub-assembly accelerated aging and (b) (4) years of finished autoinjector accelerated aging. Also, the sponsor commits to continue to perform real life aging of the final finished device to at least (b) (4) . Therefore, the provided device performance testing after accelerated aging is acceptable. The verification performance testing after accelerated aging meets the identified acceptance criteria with a (b) (4) % confidence / (b) (4) % reliability.

(b) (4)

Reviewer Comment

The sponsor has performed adequate device stability testing at accelerated aging and long-term storage conditions. The shelf life of the combination product device is (b) (4) months from the time of manufacture. The sponsor commits to continue the stability study for at least (b) (4) months. The results indicate that the device subject device continues to perform per the device specification post storage conditions.

Design verification:

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Reviewer Comment

The sponsor has performed adequate design verification testing of the Olezarsen Autoinjector 80 mg/0.8 ml configuration. The test acceptance criteria is consistent throughout the submission and the test results after preconditioning meet the performance specifications. Testing was conducted with (b) (4)% confidence and (b) (4)% reliability in results. The test results are acceptable.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has performed adequate verification and validation testing of the device constituent's Essential Performance Requirements (EPRs) per the recognized identified standards as listed above. The sponsor has performed device performance verification testing post accelerated aging and shipping pre-conditioning per the applicable referenced standards. The test results meet the performance acceptance criteria with (b)(4)% confidence / (b)(4)% reliability. Review of the device engineering performance validation/verification testing finds the sponsor's test methods and results acceptable. There are no performance deficiencies from the device perspective.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

10.FACILITIES & QUALITY SYSTEMS

10.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Reviewer Comments
A facilities inspection review has been previously completed. Please refer to the facilities inspection memo under ICCR#00988361

10.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

10.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)

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(b) (4)

Reviewer Comments

The sponsor has provided adequate summary of the manufacturing processes for the combination product. The provided information regarding the assembly processes of the autoinjector seem acceptable. (b) (4) performs the autoinjector component manufacturing, but the final assembly is performed by Ionis Pharmaceuticals at their (b) (4) . The provided information is acceptable.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

10.2.1. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

☐ Device QSR-based

☑ Drug cGMP-Based Streamline – Review Instructions

☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)

		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s):	**Reviewer Discussion –** Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Ionis Pharmaceuticals. Inc.	(b) (4)
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion –** Reviewed in Section 10.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion –** No Installation is required for this device.
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion –** No servicing is required for this device.
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion –** Reviewed in Section 10.3
Subpart H – Acceptance Activities	Firm(s):	(b) (4)

Subpart I – Nonconforming Product	Firm(s):	(b) (4)
Subpart K – Labeling and Packaging Controls	Firm(s):	

Reviewer Comments

The sponsor's provided information on the quality system sub-parts is not complete. The sponsor has not provided adequate description of how non-conforming products are handled during manufacturing and assembly of the combination product. The sponsor also has not provided adequate information on the measures taken to ensure the integrity of labeling and packaging of the products post manufacturing and storage.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☐ No

10.2.1. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)

(b) (4)

[redacted]

Reviewer Comments

The sponsor has not provided complete information regarding the CAPA investigation activities. The relevant elements do not appear to be included in the provided information. This is a deficiency.

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☐Yes	☒No

10.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g., emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Cap Removal Force	(b) (4) [redacted]	Y
Activation Force		Y
Delivered Volume		Y
Injection Time		Y
Needle Extension		Y
Needle cover lockout displacement		Y

Reviewer Comments

The sponsor has listed the above EPRs and acceptance criteria for release testing of the final finished product.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

10.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The sponsor has not provided comprehensive information regarding their CAPA procedures. This is a deficiency.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

<<END OF REVIEW>>

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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