

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219019Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



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NDA Executive Summary - Addendum

1. Application/Product Information

NDA Number.	219019		
Applicant Name	Genzyme Corporation		
Drug Product Name	QFITLIA (fitusiran)		
Dosage Form.	Injection		
Proposed Strength(s)	50 mg/0.5 mL (100 mg/mL) in a single-dose prefilled pen and 20 mg/0.2 mL (100 mg/mL) in a single-dose vial.		
Route of Administration	Subcutaneous		
Maximum Daily Dose	50 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	QFITLIA is an antithrombin-directed small interfering ribonucleic acid indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.		
Drug Product Description	50 mg/0.5 mL (100 mg/mL) in a single-dose prefilled pen and 20 mg/0.2 mL (100 mg/mL) in a single-dose vial		
Co-packaged product information	N/A		
Device information:	The pen injector in the 50 mg presentation is a device constituent.		
Storage Temperature/ Conditions	• (b) (4) for the drug product in 0.2 mL vials • 2°C to 8°C for the 0.5 mL prefilled pen injector.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Daniel Jansen	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Monica Cooper	Mohan Sapru



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	<i>Manufacturing</i>	Carl Lee	Rose Xu
	<i>Biopharmaceutics</i>	N/A	
	<i>Microbiology</i>	Sarah Davis	Neal Sweeney
	<i>Other (specify):</i>	See consult below.	
	<i>RBPM</i>	Mikee Aguirre	
	<i>ATL</i>	Theodore Carver	
Consults	CDRH consult review: Bingjie Liang and Shruti Mistry OPEQ/OHT3/DHT3C		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

- A shelf life of 36 months is granted for the 20 mg drug product in a 0.2 mL single-dose vial (100 mg/mL) when stored either at 2°C to 8°C (36°F to 46°F) or at 15°C to 30°C (59°F to 86°F).
- A shelf life of 24 months is granted for the 50 mg drug product in a 0.5 mL single-dose prefilled pen (100 mg/mL) when stored at 20°C to 80°C. The 50 mg drug product may be stored at 15°C to 30°C (59°F to 86°F) for a single period of up to 3 months at the end of storage within the shelf life of 24 months.

The expiration date for the 50 mg packaged product, Qfitlia in a single-dose prefilled pen, shall be dependent on the shortest expiration date of any component.

b. Additional Comments for Action

None. No post-marketing commitment is required.

4. Basis for Recommendation:



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a. Summary of Rationale for Recommendation:

1) Background

This review is an addendum to the previous Integrated Quality Assessment submitted on January 17, 2025.

2) Addendum to the drug product review

a. *Storage condition.*

The revised shelf life and storage conditions for both drug products, stated in section 3 above, have been approved by the drug product review team. These conditions are supported by the long-term stability data submitted for both drug products.

b. *Removal of requirement for a Post-marketing Commitment (PMC).*

After review of information provided by the Applicant in amendments submitted on February 24, 2025 and March 4, 2025 (Sequences 47 and 49), the review team, including the CDRH reviewers, concluded that a PMC is no longer required because there is adequate assurance regarding the Applicant's investigation of injection time failures of the prefilled pen injection system and supporting stability data for the proposed 24 month shelf life for this drug product presentation.

c. *Review of the addition of a new 10 mg dose (0.1 mL) proposed for the 20 mg drug product in single-dose vials.*

During the late cycle meeting with the Applicant, a new 10 mg dose was proposed by FDA and agreed to by the Applicant, for which additional information was submitted to the NDA. As the dose comprises a very small volume (0.1 mL), the drug product review team determined that additional data were needed to support dose accuracy for the 0.1 mL dose, which were provided by Applicant. and assessed to be adequate to support delivery of the proposed dose with acceptable accuracy using the proposed syringe. See the attached amendment to the drug product review.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate



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Biopharmaceutics - **N/A**
Microbiology - **Adequate**

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:

A postmarketing commitment is not required (correction to prior comments).



Theodore
Carver

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NDA Executive Summary

1. Application/Product Information

NDA Number.	219019		
Applicant Name	Genzyme Corporation		
Drug Product Name	QFITLIA (fitusiran)		
Dosage Form.	Injection		
Proposed Strength(s)	50 mg/0.5 mL (100 mg/mL) and 20 mg/0.2 mL (100 mg/mL)		
Route of Administration	Subcutaneous		
Maximum Daily Dose	50 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	QFITLIA is an antithrombin-directed small interfering ribonucleic acid indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.		
Drug Product Description	50 mg/0.5 mL (100 mg/mL) in a single-dose prefilled pen and 20 mg/0.2 mL (100 mg/mL) in a single-dose vial		
Co-packaged product information	N/A		
Device information:	The pen injector in the 50 mg presentation is a device constituent.		
Storage Temperature/ Conditions	• (b) (4) for the drug product in 0.2 mL vials • 2°C to 8°C for the 0.5 mL prefilled pen injector.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Daniel Jansen	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Monica Cooper	Mohan Sapru



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	<i>Manufacturing</i>	Carl Lee	Rose Xu
	<i>Biopharmaceutics</i>	N/A	
	<i>Microbiology</i>	Sarah Davis	Neal Sweeney
	<i>Other (specify):</i>	See consult below.	
	<i>RBPM</i>	Mikee Aguirre	
	<i>ATL</i>	Theodore Carver	
Consults	CDRH consult review: Bingjie Liang and Shruti Mistry OPEQ/OHT3/DHT3C		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 36 months is granted for the 20 mg drug product in a 0.2 mL single-dose vial (100 mg/mL) when stored at (b) (4)

A shelf life of 24 months is granted for the 50 mg drug product in a 0.5 mL single-dose prefilled pen (100 mg/mL) when stored at 2°C to 8°C.

b. Additional Comments for Action

See Post Marketing Commitment below.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, Genzyme Corporation submitted an original NDA for fitusiran, an anti-thrombin-directed small interfering ribonucleic acid (siRNA) indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients aged 12 years and older with hemophilia A or B



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with or without factor VIII of IX inhibitors. Fitusiran is a new molecular entity that has received Orphan Drug designation for treatment of hemophilia A or B and has been granted Breakthrough Therapy and Fast Track designations. Because one of the drug product presentations is a pen injector, a CDRH review team was consulted to review device aspects of the drug product, in addition to drug substance, drug product, manufacturing, and microbiology review teams from OPQ.

2) Drug Substance (fitusiran)

The drug substance, fitusiran, is the sodium salt of a synthetic double-stranded RNA oligonucleotide conjugated to GalNAc aminosugar residues. The sense strand contains 21 nucleotides and the antisense strand contains 23 nucleotides. The individual strands are synthesized (b) (4)

(b) (4). Strand purity is controlled using (b) (4)

(b) (4) The drug substance review concluded that the analytical procedures, specifications, process and controls, and stability and other supporting data are adequate to support the quality of the drug substance. The proposed retest period of (b) (4) months was determined to be supported by the stability studies.

3) Drug Product (fitusiran injection)

The drug product is supplied in two presentations: a glass vial (colorless Type (b) (4) glass) with a nominal fill volume of 0.2 mL delivering 20 mg fitusiran per injection (20 mg dose) and a 1-mL glass syringe with a nominal fill volume of 0.5 mL assembled into a prefilled pen (PFP) delivering 50 mg fitusiran per injection (50 mg dose). Single strand and double-strand purity of the drug product are analyzed using methods that are similar to the methods used for the drug substance. In response to information requests, the Applicant included a test for gross content in the drug product specification and tightened limits for force measurements to support the proposed specifications and shelf life (see also device review and post marketing commitment below). The drug product review concluded that the supporting studies, analytical procedures, specifications, stability data, and other drug product information are adequate to support the quality of the proposed commercial drug product.

4) Manufacturing

Process: The manufacturing review concluded that the manufacturing process and controls are adequate to support the quality of the drug product after the Applicant provided satisfactory responses to information requests



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concerning the in-process controls, process parameters, process times, and other information.

Facilities: The manufacturing review concluded that all facilities are adequate based on the manufacturing risk, in-process controls, and GMP compliance history.

5) Microbiology

The microbiology review concluded that the (b) (4) process, controls, drug product tests, and other supporting microbiological information are adequate to support the quality of the proposed drug product.

6) Device Aspects of the Drug Product

The device review concluded that the device aspects of the PFP device part of the drug product, including the design controls, risk management, design verification, facility and quality system information, and other device information are adequate to support the quality of the PFP drug product. During the course of the review, however, a stability issue was identified for a primary batch of the PFP drug product, where long injection times (18 to 27 seconds) were observed for < 2% of PFP samples at the 24-month time point for long-term stability studies at the proposed storage condition. The drug product and device review teams worked collaboratively in sending information requests and comments to the Applicant to ensure that the in-process tests and specified limits for device performance (for example, breakthrough and glide force acceptance criteria) are adequate to ensure the quality of the drug product and that the labeling includes adequate instructions to avoid problems with drug delivery in the event of longer injection times. Although this issue has been adequately addressed in the NDA, a post marketing commitment for the Applicant has been drafted to address this issue:

- In section 3.2.P.8.3 Stability Data Primary Stability Data – Prefilled Pen, you noted that for 1/60 pre-filled pens (PFP), a single measurement value (17.9s) at 24 months at 30°C/75%RH exceeded the specification limit, i.e., (b) (4). In the response to Request for Information Item No. 34 and No. 5b provided in sequence 0016, you identified several factors which contributed to the PFP injection time observations and proposed a revised storage direction based on the investigations. However, you have not identified the root cause for the PFP injection time observations yet. Please continue the root cause analysis to identify the underlying causes of the longer PFP injection time in order to rectify the issue at the source and prevent the issue from happening to commercial products in accordance with 21 CFR 820.100(a)(2).*



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7) Quality labeling

The drug product team reviewed the quality aspects of the labeling and concluded that is adequate to support the drug product, with final revisions to be communicated to the Applicant prior to an approval action.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	N/A
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:

Comment regarding drug product shelf life:

For the bulk prefilled syringe (bPFS)/prefilled pen (PFP) presentation of the drug product, the stability data support long-term storage at refrigerated conditions (5oC) with up to 3 months storage at room temperature (within the expiration date). The need for refrigerated long-term storage of the PFPs is due to an increase in the maximum glide force observed over time at 30oC/75% RH (the applicant's room temperature storage condition). This was first noted through the observation of 1 out of 60 PFP units having very long injection times during two stability studies at the 24-month timepoint at 30°C/75%RH. The applicant has committed to continue their investigation into the cause of the increase in maximum glide force and longer injection times and provide the data to FDA when available. For any requests to extend the overall shelf life of the drug



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product in PFPs (at refrigerated storage) or requests for an extension of the period PFPs can be held at room temperature conditions, the reviewer should request the data from the ongoing investigation.

Post Marketing Commitment:

In section 3.2.P.8.3 Stability Data Primary Stability Data – Prefilled Pen, you noted that for 1/60 pre-filled pens (PFP), a single measurement value (17.9s) at 24 months at 30°C/75%RH exceeded the specification limit, i.e., (b) (4). In the response to Request for Information Item No. 34 and No. 5b provided in sequence 0016, you identified several factors which contributed to the PFP injection time observations and proposed a revised storage direction based on the investigations. However, you have not identified the root cause for the PFP injection time observations yet. Please continue the root cause analysis to identify the underlying causes of the longer PFP injection time in order to rectify the issue at the source and prevent the issue from happening to commercial products in accordance with 21 CFR 820.100(a)(2).



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Carver

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number	219019
Assessment Cycle Number	1
Drug Product Name	Qfitlia (Fitusiran) injection

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate (with the recommended revisions)	eCTD 0001 (SD 1): 28-Mar-2024
Patient Information	Adequate (with recommended revisions)	eCTD 0001 (SD 1): 28-Mar-2024
Instruction for Use (IFU)	Adequate (with the recommended revisions)	eCTD 0001 (SD 1): 28-Mar-2024
Container Labels	Adequate (with the recommended revisions)	eCTD 0001 (SD 1): 28-Mar-2024
Carton Labeling	Adequate (with the recommended revisions)	eCTD 0001 (SD 1): 28-Mar-2024

Brief Description of Outstanding Issues: With the recommended revisions (which will be sent to the applicant during the labeling negotiations), the labeling will meet the regulatory requirements from a CMC perspective.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0001 (SD 1)	28-Mar-2024	Original package insert, patient information, instructions for use, carton, and container labels.

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

For subcutaneous use only.

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	Qfitlia (Fitusiran) Injection
Route(s) of administration	Adequate	Subcutaneous
Controlled drug substance symbol (if applicable)	N/A	Not a controlled drug substance.
Initial U.S. Approval [§201.57(a)(3)]	Adequate	The initial U.S. Approval will be for the current NDA.
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Injection 0.2 mL (20 mg) single-use vial 0.5 mL (50 mg) single-use prefilled pen (PFP)

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format \(January 2018\)](#)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format \(January 2018\)](#); USP <1151>; USP Nomenclature Guideline

⁵ [Labeling Review Tool \(March 2022, page 13\)](#), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	Adequate	The active ingredient is fitusiran sodium. The strength is based on the free acid (fitusiran).
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	Not a tablet.
For injectable drug products for parenteral 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. ⁸	Adequate	Single-dose vial and single-dose prefilled pen.

Assessment: Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Preparation and Administration Instructions

QFITLIA is intended for use under the guidance of a healthcare provider. Provide proper training to patients and/or caregivers on the preparation and administration of QFITLIA prior to use, according to the "Instructions for Use (IFU)".

⁶ Guidance: [Naming of Drug Products Containing Salt Drug Substances](#) (June 2015); MAPP 5021.1

⁷ Guidance: [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation](#) (March 2013)

⁸ Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use](#) (October 2018); USP <659>

⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format](#) (January 2023); Labeling Review Tool (March 2022, page 25)

QFITLIA for subcutaneous administration is a clear, colorless to pale yellow solution. Do not use if the solution is discolored or cloudy, or if it contains visible flakes or particles. Do not use QFITLIA if it has been dropped or damaged.

Administer subcutaneous injection into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. A caregiver can also inject QFITLIA in the outer area of the patient's upper arm. QFITLIA should not be injected into skin that is tender, damaged, bruised, or scarred. Do not inject into a vein.

¹⁰ Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate (with the recommended revisions)	Vials: In order to avoid pooling any remaining solution from different vials for further patient use, a statement to "discard unused portion of the drug" is recommended. These revisions will be sent to the applicant during the labeling mark-up.
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	Adequate	The following statement is included: <i>Do not use if the solution is discolored or cloudy, or if it contains visible flakes or particles.</i>
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	No USP monograph.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not a radioactive product.
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x"</i> with x numerical citation to "OSHA Hazardous Drugs."	N/A	Not a hazardous product.

Assessment: *Adequate* (with the recommended revisions). The recommended revisions will be negotiated during the labeling mark-up. See the issues listed above.

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

QFITLIA is a clear, colorless to pale yellow solution in a single-dose:

- Injection: 50 mg/0.5 mL pre-filled pen
- Injection: 20 mg/0.2 mL vial

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Adequate	• 0.2 mL (20 mg) single-use vial • 0.5 mL (50 mg) Pre-filled Pen (PFP)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	The active ingredient is fitusiran sodium. The strength is based on the free acid (fitusiran).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	Clear, colorless to pale yellow solution.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	Not a tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk	Adequate	Single dose vial and single-dose pre-filled pen.

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
package and imaging bulk package (see USP <659>).		

Assessment: *Adequate*. No revisions are needed to the Dosage Forms and Strengths.

(b) (4)

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	Qfitlia (Fitusiran) Injection
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Injection, Subcutaneous
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate (with the recommended revisions)	The active ingredient is fitusiran sodium. The strength is based on the free acid (fitusiran). The labeling markup will recommend the addition of the equivalent fitusiran sodium amounts for each presentation. This revision will be sent to the applicant during the labeling mark-up.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	Inactive ingredients (with amounts) are listed.

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	Inactive ingredients (with amounts) are listed. Phosphoric acid (concentrated) and sodium hydroxide may be added to adjust to pH 7.0.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	No alcohol is present.
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate (with the recommended revisions)	A statement, "Qfitlia is supplied as a sterile clear, colorless to pale yellow solution for subcutaneous administration" is included. The addition of "preservative-free" is recommended. This revision will be sent to the applicant during the labeling mark-up.
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	Revisions from the clinical division include: "an antithrombin-directed small interfering ribonucleic acid (siRNA)" for the pharmacologic/therapeutic class.
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	The molecular formula, molecular weight, and structural formula are included.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	Not a radioactive product.
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate (with the recommended revisions)	The labeling markup will recommend the addition of physical properties

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		(e.g., appearance, solution pH, solubility). This revision will be sent to the applicant during the labeling mark-up.
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	Not an oral prescription drug product.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	No promotional or misleading statements are included.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	No USP monograph.

Assessment: *Adequate* (with the recommended revisions). The recommended revisions will be negotiated during the labeling mark-up. See the issues listed above.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

QFITLIA (fitusiran) is a clear, colorless to pale yellow solution supplied in a single-dose PFP or a single-dose vial. Each pre-filled pen is designed to deliver 50 mg of QFITLIA in 0.5 mL (NDC 58468-0348-1). Each vial is designed to deliver 20 mg of QFITLIA in 0.2 mL (NDC 58468-0347-1).

50 mg Pre-Filled Pen

- Store QFITLIA at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
- QFITLIA may be stored at room temperature, (b) (4) for a single period of up to (b) (4) months within the expiration date printed on the label. After storage at room temperature, do not return the product to the refrigerator.

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

20 mg Vial

- Store QFITLIA at 2°C to 30°C (36°F to 86°F) in the original carton to protect from light.

Do not shake QFITLIA at any time. Do not heat QFITLIA. Do not freeze. Do not put into direct sunlight.

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Injection
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	The active ingredient is fitusiran sodium. The strength is based on the free acid (fitusiran)
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	• 0.2 mL (20 mg) single-use vial • 0.5 mL (50 mg) Pre-filled Pen (PFP)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Clear, colorless to pale yellow solution.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored.”	N/A	Not a tablet.
For injectable drug products for parenteral 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 (see USP <659>).	Adequate	Single dose vial and single-dose pre-filled pen.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Statements to store in the original carton to protect from light, do not shake at any time, do not heat, do not freeze, and do not put into direct sunlight are included. In addition, a statement to store the prefilled pens refrigerated is included.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate (with recommended revisions)	<u>Prefilled Pen</u>: The labeling markup includes revisions for storing the prefilled pens at USP refrigerated conditions (2 – 8°C) with a single period of up to 3 months at controlled room temperature (b) (4) In addition, the labeling markup includes a statement to discard the PFPs after 3 months storage at room temperature or at the expiration date, whichever comes first. <u>Vial</u>: Revisions are also included for storing the vials at USP controlled room temperature conditions (b) (4) (b) (4) (b) (4) 15 – 30°C (59 – 86°F). These revisions will be sent to the applicant during the labeling mark-up.
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	N/A	No latex is used.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
<i>made with natural rubber latex. Avoid statements such as "latex-free."</i> ²¹		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	Not applicable.

Assessment: *Adequate* (with the recommended revisions). The recommended revisions will be negotiated during the labeling mark-up. See the issues listed above.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	The following is included: Genzyme Corporation Cambridge, MA 02141

Assessment: *Adequate*

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool](#) (March 2022, page 74)

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(b) (4)

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	Qfitlia (Fitusiran) Injection
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate (with the recommended revisions)	The storage statement in the Medication Guide and Instructions for Use should be revised to follow the revised storage statement in the package insert.

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
		This revision will be sent to the applicant during the labeling mark-up.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	No desiccant included.
Active ingredient(s) (if applicable).	Adequate	fitusiran
Alphabetical listing of inactive ingredients (if applicable).	Adequate	dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, phosphoric acid, sodium hydroxide, and Water for injection, USP
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Genzyme Corporation Cambridge, MA 02141 1-800-745-4447

Assessment: *Adequate* (with the recommended revisions). The recommended revisions will be negotiated during the labeling mark-up. See the issues listed above.

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Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Qfitlia (fitusiran) injection
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	20 mg / 0.2 mL (vial) 50 mg / 0.5 mL (PFP)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	Subcutaneous administration
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate (with the recommended revisions)	Yes	The addition of fitusiran "(equivalent to X mg of fitusiran sodium)" will be recommended for each presentation. This revision will be sent to the applicant during the labeling mark-up.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate (with the recommended revisions)	Yes	The storage statement on the container and carton labels should be revised to follow the revised storage statement in the package insert. (b) (4) <u>Prefilled Pen:</u> (1) A line should be added to the PFP carton label (and the PFP container label, if sufficient space is available) for the date when the PFP is taken out of the refrigerator. (2) A statement that the product should be stored in the original carton to protect from light is recommended. These revisions will be sent to the applicant during the labeling mark-up.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk	Adequate	Yes	Carton and container labels include "single dose" and "for subcutaneous use only."

Item	Item in Proposed Carton Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Is item in Container Labels same as that of Carton Labeling?	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
package and imaging bulk package, and these products require a “Not for direct infusion” statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	No	Carton labels list inactive ingredients. Container labels do not list inactive ingredients due to limited space.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	No	Carton labels list inactive ingredients (with amounts). Container labels do not list inactive ingredients due to limited space. Phosphoric acid and sodium hydroxide may be added to adjust pH.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	Alcohol is not present.
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Yes	
Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Adequate	No	Carton label states, “Dosage and Administration: See full prescribing information.”
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	Genzyme Corporation Cambridge, MA 02141
“Keep out of reach of children” statement, optional for Rx,	Adequate	Yes	

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	No	Carton label states, "Attention: Dispense with Medication Guide."
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	Adequate	Yes	No text on protective cap of vial.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	No USP monograph.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹	N/A	Yes	No USP monograph.
And others if space is available.	N/A	Yes	N/A

Assessment of Carton Labels and Container Labeling: *Adequate* (with the recommended revisions). The recommended revisions will be negotiated during the labeling mark-up. See the issues listed above.

³¹ USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

All recommended revisions will be sent to the applicant during the labeling mark-up. See the issues listed above. With these revisions, the labeling information will comply with the regulatory requirements from a CMC perspective.

Primary Drug Product Assessor Name and Date:

Monica D. Cooper, Ph.D. (See Panorama for date.)

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

Mohan Sapru, Ph.D. (See Panorama for date.)



Monica
Cooper

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Mohan
Sapru

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Title:	NDA IQA Template CHAPTER VII-MICROBIOLOGY		
Document ID:	OPQ-ALL-TEM-0048		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	79		



Template Revision: 03

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see [Chapter VII \(Microbiology\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

Product Information	Fitusiran
NDA Number	219019
Assessment Cycle Number	01
Drug Product Name/ Strength	Qfitlia (Fitusiran)
Route of Administration	Subcutaneous
Applicant Name	Genzyme Corporation
Therapeutic Classification/ OND Division	Division of Non-malignant Hematology
Manufacturing Site	<u>Fitusiran drug product in vials</u> Vetter Pharma-Fertigung GmbH & Co. KG Eisenbahnstrasse 2-4 88085 Langenargen, Germany FEI No.: 3002808846 <u>Fitusiran drug product prefilled pens (PFP)</u> Vetter Pharma-Fertigung GmbH & Co. KG Schuetzenstrasse 87 and 99-101 88212 Ravensburg, Germany FEI No.: 3002270322
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is acceptable and does not require additional information or amending prior to approval.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001	3/28/2024
0005	5/07/2024
0007	5/14/2024
0016	08/27/2024
0024	10/04/2024
0031	10/28/2024
0033	11/05/2024

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: The drug product is a sterile liquid contained in a single-dose vial or syringe. Fitusiran (Qfitlia) is used to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia A with or without inhibitors.

Concise Description of Outstanding Issues (*list bullet points with key information and update as needed*):

(none)

Supporting Documents:

DMF# (b) (4) Contains information regarding (b) (4) depyrogenation validation.

DMF # (b) (4) Describes both the depyrogenation and sterilization of the (b) (4) product.

S DRUG SUBSTANCE

3.2.S.4.1 "Specification"

The drug substance (Fitusiran) manufacturing processes are not the subject of this product quality microbiology review as the drug substance is not prepared sterile.

Assessment: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

3.2.P.1 "Description and Composition of the Drug Product"

Fitusiran (the drug product, or DP) for subcutaneous administration (100mg/mL) is an aqueous, sterile, clear solution. The drug product is supplied in two presentations:

- Vial with a nominal fill volume of 0.2 mL drug product solution.
- Prefilled pen (PFP) with a nominal fill volume of 0.5 mL drug product solution.

Table 1 Composition of fitusiran - solution for injection – 100 mg/mL

Components ^a	Composition			Function	Reference to standards ^b
	Per mL [mg]	Per unit (vial) [mg]	Per unit (PFP) [mg]		
Fitusiran [equivalent to fitusiran sodium]	100 [106.0]	20 [21.2]	50 [53.0]	Drug substance	In-house
Sodium chloride	4.909	0.982	2.455	(b) (4)	Ph. Eur., USP/NF
Dibasic sodium phosphate ^c	1.169	0.234	0.585		Ph. Eur., USP/NF
Monobasic sodium phosphate ^d	0.0885	0.0177	0.0443		USP/NF
Phosphoric acid, concentrated [Phosphoric acid]	q.s. pH 7.0	q.s. pH 7.0	q.s. pH 7.0	Acidifying agent	Ph. Eur., USP/NF
Sodium hydroxide	q.s. pH 7.0	q.s. pH 7.0	q.s. pH 7.0	Alkalizing agent	Ph. Eur., USP/NF
Water for injection	q.s. 1 mL	q.s. 0.2 mL	q.s. 0.5 mL	Solvent	Ph. Eur., USP/NF

(b) (4)

a Components are listed according to their pharmacopoeia names, if available. If more than one monograph exists, other names are given in brackets, along with the compendial origin.

b Reference is made to the current edition of the Pharmacopoeia.

c (b) (4).

d (b) (4).

e Not contained in the finished product.

Description of Container Closure System

3.2.P.7 “Container Closure System – Vial, 20mg” and “Container Closure System – PFP, 50mg”

Packaging component	Description	Supplier
Vial		
Container	(b) (4)	
Stopper		
1 mL Syringe		
Plunger/ stopper	(b) (4)	
Syringe		
Staked needle (b) (4)G 1/2")		
(b) (4)		
Rigid cap		

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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

Date	12/5/2024		
To:	MIKEE AGUIRRE		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Choose an item.
From	Bingjie Liang OPEQ/OHT3/DHT3C		
Through (Team)	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 219019, FITUSIRAN ICC# 2400425 ICCR# 00988392		
Recommendation	Filing Recommendation Date: 5/10/2024 ☐ 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: 8/14/2024 ☐ 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: 12/5/2024 ☐ 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)
Bingjie Liang -S Digitally signed by Bingjie Liang -S Date: 2024.12.05 15:41:06 -05'00'	Shruti N. Mistry -S	2024.12.05 15:49:21 -05'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 219019
Sponsor	Genzyme Corporation
Drug/Biologic	FITUSIRAN
Indications for Use	* Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia A with and without inhibitors * Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia B with and without inhibitors
Device Constituent	Auto-Injector
Related Files	ICCR#00988771, ICCR#00988404

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

Important Dates	
Discipline-Specific Review Memos Due	n/a
Final Lead Device Review Memo Due	10/22/2024
Interim Due Dates	Meeting/Due Date
Filing	5/10/2024/5/15/2024
74-Day Letter	6/11/2024
Mid-Cycle	8/28/2024
Primary Review	1/13/2024
Internal Meeting(s)	Mid-cycle Meeting 8/28/2024
Sponsor Meeting(s)	Mid-cycle Meeting 9/17/2024

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 <u>Notes</u>
	Yes	No	NA	
<u>Device Description</u>	x			The sponsor provided a description of PFP constituent design, including drawing/diagrams and the principle of operation. It appears adequate.
<u>Labeling</u>	x			The sponsor provided carton and container labels, and Instruction for Use (IFU). The IFU is consistent with the device functions of the combination product. The full review of the labeling is deferred to CDER.
<u>Design Controls</u>	x			The sponsor has provided the justification that the cap and cap lid color change after the clinical trials have no impact on the safety or effectiveness of the PFP. The sponsor has provided the executed registration batch records in the response provided in sequence 0016 and indicated that the executed batch record for the batch used for primary stability is representative for commercial batches. However, the sponsor has not provided the proposed commercial master batch record (MBR) for the finished PFP assembly in the submission. The MBR is a reference document that ensures consistency and quality in production, while the Executed Batch Record (EBR) documents the execution of the process. An Information Request (IR) is issued to request MBR. The sponsor has provided the traceability between design requirements, risk control measures and verification and validation activities in the response provided in sequence 0016.
<u>Risk Analysis</u>	x			The risk management activities have been performed throughout the development of the PFP in accordance with the process outlined in ISO 14971:2019. The sponsor provided the individual residual risk and overall residual risk associated, and the hazard list within the Risk Analysis Report.
<u>Design Verification</u>	x			Results of the PFP functional performance tests conducted according to ISO 11608 met the acceptance criteria. The sponsor provided the test methods and methods validation in sequence 0037.

				Test results of the accelerated aging study were within the specifications. For stability study, the sponsor noted that “one single measurement value (17.9s) out of 60 test samples exceeds specification limits ((b) (4)). Root cause analysis is ongoing at the time of submission”. Sharps injury prevention simulated use study was conducted on 18 users (9 adult lay users and 9 registered nurses) activated 500 production equivalent devices and confirmed successful actuation and locking by pressing the needle cover. The PFP contact with the user is limited to the skin for a limited (≤ 24 hour) contact duration. The materials of the PFP components, i.e., (b) (4) are listed in Appendix G of the guidance. No further biological testing is needed in accordance with ISO 10993-1, section 4.1. It appears adequate. The shipping simulation study was conducted for both devices packed on a pallet and devices packed in shipping boxes. Results all device EPRs were met after shipping. It appears acceptable. Design validation studies are maintained in the Design History File (DHF), including human factors Clinical Overview. The design validation establishes that the PFP meets all the documented user needs and supports safe and effective use by the intended user population. CDRH defers the PFP clinical experience review to CDER/Clinical.
<u>Consultant Discipline Reviews</u>			x	
<u>Clinical Validation</u>			x	Over 600 injections have been completed using the 50 mg fitusiran PFP in clinical study LTE15174 provided in section 2.5. Clinical Overview. CDRH defers clinical validation review to CDER/clinical.
<u>Human Factors Validation</u>			x	Human factors summative validation study (HFVS) was conducted on 5 user groups consisting of users for a total of 75 participants. The HFVS did not result in use errors, close calls, or difficulties on critical tasks that would result in harm to the intended users for risks that could be further reduced by modifications to the user interface. CDRH defers HFVS review to CDER/DMEPA.
<u>Facilities & Quality Systems</u>	x			No inspection is required. The quality system information is adequate.

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 #:

- a. CDRH defers clinical validation review to CDER/clinical.
- b. CDRH defers Human Factors Validation Study review to CDER/DMEPA.

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:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market <u>Commitments or Requirements</u>	☒
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

- In section 3.2.P.8.3 Stability Data Primary Stability Data – Prefilled Pen, you noted that for 1/60 pre-filled pens (PFP), a single measurement value (17.9s) at 24 months at 30°C/75%RH exceeded the specification limit, i.e., (b) (4). In the response to Request for Information Item No. 34 and No. 5b provided in sequence 0016, you identified several factors which contributed to the PFP injection time observations and proposed a revised storage direction based on the investigations. However, you have not identified the root cause for the PFP injection time observations yet. Please continue the root cause analysis to identify the underlying causes of the longer PFP injection time in order to rectify the issue at the source and prevent the issue from happening to commercial products in accordance with 21 CFR 820.100(a)(2).

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3. PURPOSE/BACKGROUND

3.1. Scope

Genzyme Corporation is requesting approval of FITUSIRAN. The device constituent of the combination product is an Auto-Injector. The sponsor notes that the term “prefilled pen (PFP)” may be used synonymously with the term autoinjector (AI) in section 2.3.P.1.

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

Please review the Pre-Filled Pen (PFP) device for commercial marketing approval, including the description, design, development, manufacturing, control, transportation and aging studies, and combination quality system information to determine if the PFP is acceptable from a CDRH perspective.

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
- Design verification
- Design validation
- Performance requirements
- Stability
- Shipping
- Control strategy
- Facility and Quality system

This review will not cover the following review areas:

Human Factor Study
Clinical Study

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

ICCR 00988771 Request submitted.

- Please provide the regulatory status of the CDx antithrombin (AT) assay do be used with fitusiran.
- Could CDRH confirm the adequacy of the Applicant's proposal (b) (4)
[REDACTED]
- Does CDRH agree with (b) (4)?
[REDACTED]

ICC2400496 Request details:

Fitusiran solution for injection 100mg/ml is supplied in a vial and a prefilled pen for life saving treatment. The prefilled pen is a drug-device combination product intended for self-administration. Please advise if a PAI is needed for the device assembly facility.

3.3. Indications for Use

Combination Product	Indications for Use
FITUSIRAN	* Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia A with and without inhibitors * Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia B with and without inhibitors
Auto-Injector	<u>Delivery of the Drug Product</u>

3.4. Materials Reviewed

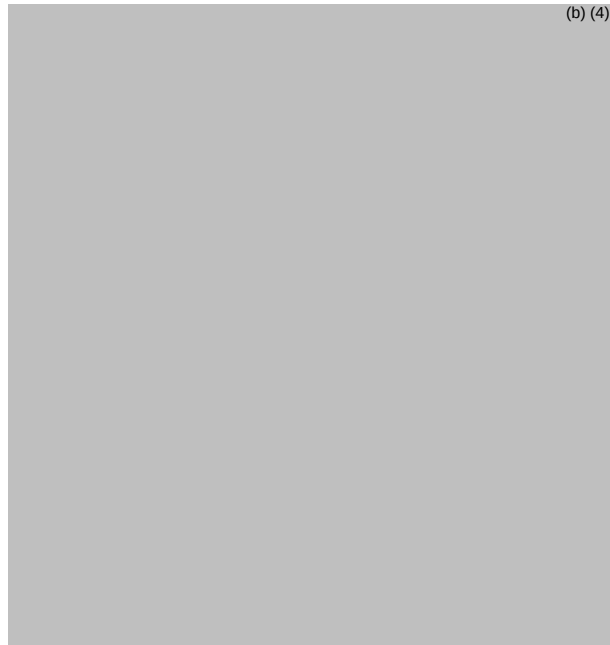
<u>Materials Reviewed</u>	
Sequence	Module(s)
0001	1.4.1, 1.14, 1.16
	3.2.P.2, 3.2.P.3, 3.2.P.5, 3.2.P.7, 3.2.P.7, 3.2.P.8
	3.2.R
0016	1.11
	3.2.R
0037	1.11

4. DEVICE DESCRIPTION

4.1. Device Description

4.1.1 Design Feature

The PFP is provided fully assembled with the bulk PFS containing 0.5 mL of fitusiran solution for injection 100 mg/mL drug product (DP). The PFP is designed to deliver a minimum volume of 0.5 mL fitusiran solution for a 50 mg dose and is self-disabling to prevent re-use. Figure 1 shows the PFP both before and after injection. The PFP window provides for visibility of the bulk PFS and drug product solution, as well as confirmation of injection completion via the yellow indicator.



The design features of the PFP are shown in Table 1.

Table 1 - Fitusiran PFP description

Item	Feature/Specification
Usage	Single-use
Conditions of use	Self-administration, caregiver and HCP administration
Injection sites	Abdomen, thigh, upper arm
Injection tissue	Subcutaneous
Injector mechanism	Mechanical, spring-powered (no electronic components)
Needle attachment	Pre-attached
Needle insertion/removal	Manual
Activation method	Buttonless, push activation
Feedback mechanism	Audible, visual
Needle protection	The needle cover shields the needle before use. The needle cover locks in place after the user removes the PFP from the injection site, preventing further access to the needle. The needle is hidden from view throughout the injection process.

4.1.2 Container closure system components

The major components of the fitusiran PFP container closure system consist of the bulk PFS as the primary container closure system with direct product contact and the PFP subassemblies and PFP cap lid without product contact as shown in Figure 2.

Figure 2 - Prefilled pen components and subassemblies



4.1.3 Prefilled pen components and materials of construction

A representative exploded view of the PFP is provided in Figure 3. The components and materials of construction for the PFP components that may come into direct contact with the user are presented in Table 2.

Figure 3 - Exploded view PFP components



Table 2 - Prefilled pen components and materials of construction in contact with user

Component	Material	Subassembly	Color
Cap	(b) (4)	Front	Blue
Needle cover		Front	Orange
Body		Front	White
Drive spring holder		Rear	White
Cap lid		N/A	Blue
(b) (4)			

4.1.4 Prefilled pen dimensions

Figure 4 provides engineering drawings of the PFP, while Table 3 lists the respective dimensions.

Figure 4 - Engineering drawing of the PFP



Table 3 - Dimensions of the PFP

Item	Designation	Dimension
A	Width	25 mm
B	Length	148 mm

4.2. Steps for Using the Device

The handling steps for using the PFP are cap removal, activation, end of injection, and removal of PFP from the injection site; followed by disposal of the PFP. A summary of the instructions for using the PFP is provided below:

- **Cap removal:** The user pulls the cap off. The needle shield of the bulk PFS comes off with the cap, but the needle remains hidden by the orange needle cover.
- **Activation:** The user places the orange needle cover end of the PFP perpendicular to bare skin. The user presses the PFP firmly against the skin and continues holding in place. When the needle cover is pressed against the skin, the needle is inserted, and the automatic delivery of the dose is triggered. An audible click sound indicates the start of injection, and the window will start to turn yellow.
- **End of Injection:** The user should watch the window turn completely yellow as the plunger advances, indicating completion of injection. Completion of injection is secondarily indicated by a second audible click.

- Removal of PFP from the Injection Site: The user lifts up the PFP to remove it from the skin. The needle cover automatically extends over the needle and locks into position to protect from sharps injury and prevent re-use.

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 sponsor provided a description of PFP constituent design, including drawing/diagrams and the principle of operation. It appears adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		x		
Device Constituent Labeling		x		
Letters of Authorization		x		
Essential Performance Requirements defined by the application Sponsor		x		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		x		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		x		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		x		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		x		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	x		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	x		
	Reliability	x		
	Biocompatibility	x		
	Sterility			x
	Software			x
	Cybersecurity			x
	Electrical Safety			x
	EMC/RF Wireless			x
	MR Compatibility			x

	Human Factors	x		
	Shelf Life, Aging and Transportation	x		
	Clinical Validation	x		
	Human Factors Validation	x		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	x		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	x		
	CAPA Procedure	x		
	Control Strategy provided for EPRs	x		

Reviewer Comment

The sponsor provided the following information related to the PFP. The device constituent content in the submission for the combination product is acceptable for filling.

- Device description documentation
- Design control (21 CFR 820.30)
- Essential Performance
- Stability
- Shipping
- Control Strategy
- Quality System

5.2. Facilities Information

Firm Name:	Sanofi-Aventis Deutschland Gmb
Address:	Industriepark Höchst, Brüningstrasse 50 65926 Frankfurt am Main, Germany
FEI:	FEI: 3003195501
Responsibilities:	The firm is responsible for assembly, labeling, secondary packaging, batch release, release testing and stability testing of Pre-filled Pen (PFP).

Inspectional History

An analysis of the firm's inspection history over the past 10 years:

☒ Inspection was conducted 12/7/2015 to 12/10/2015. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A – the manufacturing site does not require an inspection at this time given the risk of the combination product.

Inspection Recommendation:

☐ A choose an item inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

A recent medical device inspection of the firm Choose an item.

☒ An inspection is not required because A recent medical device inspection of the firm was acceptable. Please refer to ICC#2400496 Facility Review Memo for more details.

Firm Name:	Genzyme Corporation
Address:	11 Forbes Road, Northborough, Massachusetts (MA) 01532, USA
FEI:	FEI: 3009389940
Responsibilities:	The firm is responsible for labeling, secondary packaging, and batch release of Pre-filled Pen (PFP). Based on the responsibilities, the site is then subject to applicable QS requirements.

Inspectional History

An analysis of the firm's inspection history over the past 11 years:

☒ Inspection was conducted 4/1/2013 to 4/9/2013. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A – the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

☐ A choose an item inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

A recent medical device inspection of the firm Choose an item.

☒ An inspection is not required because A recent medical device inspection of the firm was acceptable.

The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/Aes, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK

Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment The previous medical device inspection in 2015 was classified NAI. The most recent FDA inspection conducted in 2019 was a post-approval and GMP, and classified VAI. The post-approval inspection covered a similar prefilled pen product and did not reveal any significant discrepancies and was found acceptable. The MDSAP audit in 2023 covered design and development, manufacturing, and distribution of drug application devices. MDSAP audit identified eight minor nonconformities. No inspection is required based on the benefit-risk analysis per SOP # (b) (4). Please refer to ICC#2400496 Facility Review Memo for details.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☒ No Inspection ☐ N/A	
Site(s) needing inspection: N/A	
<u>Reviewer Comments</u>	
Filling is acceptable.	
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☒ No ☐ N/A	

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 to CDER/DMEPA		
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
<u>MRI</u> Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

- Qfitlia-50mg-0.5mL-1ct-PFP-container in 1.14.1.3

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

Reviewer Comments

The sponsor provided 0.5mL-1ct-PFP container and carton and labels in section 1.14.1.1, and Instruction for Use (IFU) in section 5.3.5.4 – Other study reports – Human factors validation summary report. The IFU is consistent with the device functions of the combination product. The full review of the labeling is deferred to CDER.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Device label	x		
Carton packaging label	x		
Instructions for use	x		

Reviewer Comments

The sponsor provided complete Labelling for the Device Constituent. The provided labeling is appropriate for the device type. The instructions for use appear clear and risks associated with each user step were mitigated. CDRH defers the review for adequacy of the device labeling to CDER/DMEPA.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by

- ☐ Insert Consultant Name ; The full memo is located in [Appendix B.](#)
- ☐ The Lead Reviewer

Below is a summary of the review & recommendation:

n/a

6.4. 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
<u>Reviewer Comments</u> The provided labeling is appropriate for the device type. A usability review of the instructions and device design is deferred to 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		

9 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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
Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products (2013)	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																
<u>Reviewer Comments</u> The sponsor provided design documentation, and recognized standards and FDA guidance. The sponsor indicated that the only modification made to the PFP after the clinical trials was changing the color of the cap and cap lid and concluded that the change has no impact on the safety or effectiveness of the PFP and was made for branding purposes and to distinguish between clinical and commercial PFPs. The user will come in direct contact with the materials of the cap and cap lid of the PFP. The sponsor should provide the supporting data, e.g., Material Safety Data Sheet of colors, to justify it. It is addressed in Filing review. The sponsor didn't mention the traceability in the submission. We recommend providing a traceability matrix to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the EPRs are highlighted for ease of review. While a traceability matrix can take many forms, the Agency has provided a high-level example for reference: <table border="1" style="margin: 10px auto; border-collapse: collapse; text-align: center;"> <thead> <tr> <th>Patient / User Needs</th> <th>Design Input(s)</th> <th>Design Output(s)</th> <th>Verification</th> <th>Validation</th> <th>Shelf Life / Stability (Y/N)*</th> <th>Shipping (Y/N)*</th> <th>Lot Release (Y/N)*</th> </tr> </thead> <tbody> <tr> <td style="height: 20px;"></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> These have been addressed in section 7.1 Design Control Summary of Design Control Activities Reviewer Comments.			Patient / User Needs	Design Input(s)	Design Output(s)	Verification	Validation	Shelf Life / Stability (Y/N)*	Shipping (Y/N)*	Lot Release (Y/N)*								
Patient / User Needs	Design Input(s)	Design Output(s)	Verification	Validation	Shelf Life / Stability (Y/N)*	Shipping (Y/N)*	Lot Release (Y/N)*											
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No																		

8. RISK ANALYSIS

8.1. Risk Management Plan

8.3. 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
<u>Reviewer Comments</u> The risk analysis is adequate.		
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

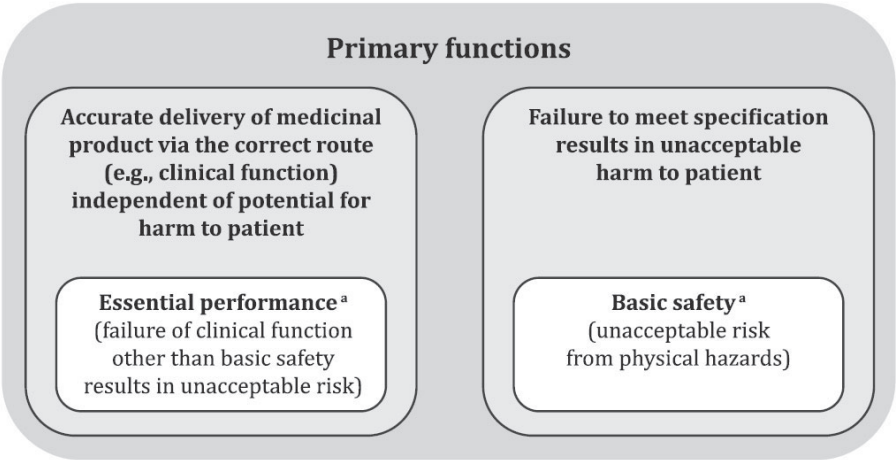
Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap removal force	(b) (4)	Y	N	Y	Y
Actuation force		Y	Y	Y	Y
Needle extension		Y	Y	Y	Y
Needle extension at the start of injection		Y	N	Y	Y
Delivered volume (dose accuracy)		Y	Y	Y	Y
Injection time		Y	Y	Y	Y
Needle cover lock override force		Y	N	Y	Y
Sharps injury protection (needle shielding after injection)		Y	N	Y	Y
Indication at end of injection by visual means (injection completion indication)		Y	Y	N	N
Container closure integrity		Y	Y	Y	Y

Reviewer Comment

The sponsor stated that the PFP design requirements in Table 5 in section 3.2.R.3. Medical Device-PFP were set based on safety, usability, and regulatory considerations. The acceptance criteria factor user requirements and the intended use of the fitusiran PFP which are derived from a risk assessment of the product design requirements and performance functions.

The sponsor didn't identify Essential Performance Requirements (EPRs). Essential performance is performance of a clinical function, other than that related to basic safety, where loss or degradation beyond the limits specified by the manufacturer results in an unacceptable risk per IEC 60601-1.

ISO 11608-1:2022 illustrated the relationship of primary functions to essential performance and basic safety from IEC 60601-1 as follows.



^a Defined in IEC 60601-1.

Prefilled pen requirements in Table 5 include EPRs and basic safety functions. All prefilled pen requirements were verified as shown in Table 7. Among the prefilled pen requirements, Actuation force, Needle extension, Delivered volume (dose accuracy), and Injection time are EPRs because failure to meet these four requirements is a failure to accurately deliver the medicinal product via the correct route. Actuation force, Needle extension, Delivered volume (dose accuracy), and Injection time are included in the PFP release specifications.

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Table 5 - PFP product requirements

Product Requirement	Requirement Description	Acceptance Criteria	Justification
Cap removal force	Force needed to remove the cap from the PFP.	(b) (4)	Cap removal is predominantly powered by shoulder and upper arm strength. Grip strength which is required to translate this power to the device is considered to be the "weakest link" when analyzing the strength requirements for PFP handling. Consolidating grip strength data from literature (1), (2). It is evident that the grip strength of 10–12-year-old girls is at the same level or higher when compared with women aged 60 years and older. In two human factors formative studies, 46 participants (50% female, 56% in age group 60-77) with dexterity impairments (arthritis) were able to remove the cap from prototypes for which the cap removal force was designed to be at the upper specification limit (b) (4). The established upper limit of (b) (4) (b) (4). A lower limit of (b) (4) has been set to safeguard the device against unintentional removal of the cap and premature exposure of the needle.
Actuation force	Force required to press in the needle cover to activate injection mechanism.	(b) (4)	Actuation force is predominantly powered by shoulder and upper arm strength. Grip strength which is required to translate this power to the device is considered to be the "weakest link" when analyzing the strength requirements for PFP handling. Consolidating grip strength data from literature (1), (2). It is evident that the grip strength of 10–12-year-old girls is at the same level or higher when compared with women aged 60 years and older. In two human factors formative studies, 46 participants (50% female, 56% in age group 60-77) with dexterity impairments (arthritis) were able to activate the device using prototypes for which the actuation force was designed to be at the upper specification limit (b) (4). The acceptance criterion is aligned with acceptable human downward push performance data based on U.S. military standard (MIL-STD-1472G), and accounting for appropriate reductions for females and elderly (applied from literature (3)). To safeguard the PFP against unintended activation, a minimum activation force of (b) (4) is necessary. (b) (4)
Needle extension	Length of needle that extends beyond the PFP during injection	(b) (4)	The acceptance criterion was established to ensure injection into the subcutaneous space, given the skin and subcutaneous space thicknesses for the population. The lower limit of the needle extension specification is (b) (4) to ensure needle penetration past the skin and into the subcutaneous layer. The upper limit of the needle extension specification is (b) (4) to reduce the risk of intra-muscular injections. Additionally, the needle extension acceptance criteria were compared against predicate devices for subcutaneous injection. The PFP combination products for comparator products also have a (b) (4) mm limit for injection depth. (4)

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Product Requirement	Requirement Description	Acceptance Criteria	Justification
Needle extension at the start of injection	Length of needle that extends beyond the PFP when the first fluid drop is initially expelled from the needle tip during the injection	(b) (4)	This requirement relates to the needle extension when the first fluid drop is expelled and before the needle is fully extended, only a lower limit is applied. The lower limit is consistent with the acceptance criteria for Needle Extension, ensuring that the full dose is within the needle extension criteria.
Delivered volume (dose accuracy)	Accuracy of the volume of drug product delivered from the PFP		The acceptance criteria is set to ensure that the dose delivered is not less than the labeled volume and that the provided dose is administered. Testing for needle extension at the start of injection fulfills the ISO 11608 requirement for assessing dose accuracy at the specified injection depth.
Injection time	Time required to expel the entire dose		An upper limit of (b) (4) was established based on design assessment data and is sufficient time to ensure that a full dose is injected.
Needle cover lock override force	Compression force required to override the locked out needle cover		A minimum force requirement of (b) (4) has been established to over-ride the needle cover deployed after the PFP injects. This safety requirement is intended to prevent the needle from being accidentally exposed after-use. ISO 11608-5 specifies that the lockout feature must withstand a load at least twice that of the maximum activation (i.e., actuation) force (b) (4). (b) (4) provides a safety margin over the minimum acceptable override force limit (b) (4).
Sharps injury protection (needle shielding after injection)	Distance between the needle tip and the edge of the locked out needle cover		A minimum of (b) (4) mm distance after injection between the locked needle cover and the needle tip has been established to ensure prevention of sharps injury by the patient, user or a third party. In accordance with ISO 23908, this specification corresponds to the distance that a sphere with a radius of 6 mm can reach inside of the PFP needle cover when resting on the needle cover. Based on design verification testing, there is at least 6.1 mm of distance between the needle tip and edge of the locked out needle cover, so the minimum acceptance criteria of (b) (4) mm provides sufficient safety factor.
Indication at end of injection by visual means (injection completion indication)	Visual inspection of the yellow indicator in the window	Yellow indicator is visible	To ensure users can confirm injection completion by visual means.
Biocompatibility	PFP is biocompatible	Compliance with ISO 10993	To assure PFP biocompatibility.

The PFP functional performance testing was conducted according to ISO 11608-1, and results were provided in Table 7 in section 3.2.R.3. Medical Device-PFP. All acceptance criteria were met. The proposed specifications for the PFP function performance are comparable to the similar autoinjector combination products, which appear reasonable.

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Table 7 - Summary of PFP functional performance testing

PFP Test	Acceptance Criteria	Data Summary							Test Results
		Standard (n=60)	Cool (n=60)	Warm (n=60)	Freefall (n=30)	Vibration (n=20)	Dry Heat (n=60)	Cold Storage (n=60)	
Cap removal force	(b) (4)	Mean: 23 N SD: 1.7 N	Mean: 27 N SD: 3.2 N	Mean: 15 N SD: 1.5 N	Mean: 23 N SD: 1.9 N	Mean: 20 N SD: 1.6 N	Mean: 20 N SD: 1.9 N	Mean: 21 N SD: 1.5 N (b) (4)	Pass
Actuation force		Mean: 10 N SD: 0.3 N	Mean: 11 N SD: 0.2 N	Mean: 10 N SD: 0.2 N	Mean: 11 N SD: 0.5 N	Mean: 10 N SD: 0.2 N	Mean: 10 N SD: 0.2 N	Mean: 10 N SD: 0.2 N (b) (4)	Pass
Needle extension		Mean: 7 mm SD: 0.2 mm	Mean: 6 mm SD: 0.1 mm	Mean: 6 mm SD: 0.1 mm	Mean: 7 mm SD: 0.2 mm	Mean: 6 mm SD: 0.1 mm	Mean: 6 mm SD: 0.1 mm	Mean: 6 mm SD: 0.1 mm (b) (4)	Pass
Needle extension at the start of injection		Mean: 5 mm SD: 0.2 mm	Mean: 5 mm Std. Dev: 0.1 mm	Mean: 4 mm Std. Dev: 0.1 mm	Mean: 5 mm SD: 0.2 mm	Mean: 5 mm SD: 0.1 mm	Mean: 4 mm SD: 0.1 mm	Mean: 5 mm SD: 0.1 mm (b) (4)	Pass
Delivered volume (dose accuracy)		Mean: 0.5 mL SD: 0.01 mL	Mean: 0.5 mL SD: 0.00 mL	Mean: 0.5 mL SD: 0.01 mL	Mean: 0.5 mL SD: 0.01	Mean: 0.5 mL SD: 0.01 mL	Mean: 0.5 mL SD: 0.01 mL	Mean: 0.5 mL SD: 0.01 mL (b) (4)	Pass
Injection time		Mean: 3 s SD: 0.2 s	Mean: 4 s SD: 0.4 s	Mean: 2 s SD: 0.2 s	Mean: 3 s SD: 0.2 s	Mean: 2 s SD: 0.2 s	Mean: 2 s SD: 0.3 s	Mean: 3 s SD: 0.2 s (b) (4)	Pass
Needle cover lock override force		Mean: 226 N SD: 2.4 N	Mean: 234 N SD: 2.1 N	Mean: 210 N SD: 2.2 N	Mean: 221 N SD: 1.8 N	Mean: 233 N SD: 2.3 N	Mean: 229 N SD: 2.8 N	Mean: 226 N SD: 2.2 N (b) (4)	Pass
Sharps injury protection (needle shielding after injection)		Mean: 6.5 mm SD: 0.15 mm	Mean: 6.9 mm SD: 0.09 mm	Mean: 6.9 mm SD: 0.09 mm	Mean: 6.5 mm SD: 0.15 mm	Mean: 6.9 mm SD: 0.06 mm	Mean: 6.9 mm SD: 0.08 mm	Mean: 6.9 mm SD: 0.09 mm (b) (4)	Pass
Indication at end of injection by visual means (injection completion indication) ^a	Yellow indicator is visible	Conforms	NT	NT	NT	NT	NT	NT	Pass
Visual inspection	No observed defects that may impact safe functioning	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Pass

^a Conducted on one representative sample at standard atmosphere to support the technical assessment.

TL range, tolerance limit (lower tolerance limit (LTL) to upper tolerance limit (UTL)); SD = standard deviation; NT: Not tested

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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 addressed the deficiencies for design verification in the mid-cycle review.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

9.3. Discipline Specific Sub-Consulted Review Summary

- ☒ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☒ There is no device related clinical studies for review
☐ There are clinical studies for review

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

12. FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

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

12.2. Quality Systems Documentation Review

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

12.3. Control Strategy Review

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

Essential Performance Requirements Control Strategy Table

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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
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12.4. 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
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Reviewer Comments

Sanofi-Aventis Deutschland GmbH (FEI: 3003195501) is responsible for assembly, labeling, secondary packaging, batch release, release testing and stability testing of Pre-filled Pen (PFP). The facility review was conducted in ICC# ICC#2400496. Based on the firm responsibility and inspection history, benefit-risk analysis, no inspection is required Per SOP # (b) (4).

The sponsor states that Sanofi is the design owner and manages the suppliers for the development and manufacturing of the device constituent part assembly units under its quality system based on applicable sections of current versions of ISO13485, the FDA Quality System Regulations 21 CFR Part 820 on page 42 in section 3.2.R.3. Medical Device-PFP.

The following IR was issued in Mid Cycle review.

- *You have indicated that you are implementing a medical device-based Quality System streamlined approach. As such you are responsible for demonstrating that your product conforms to the requirements under 21 CFR Part 820. Additionally, per the regulations under 21 CFR Part 4, Subpart A “CGMPs for Combination Products,” you are required to provide information to demonstrate adherence with specific regulations under the drug “current Good Manufacturing Practice (cGMP)” regulations (21 CFR Part 210 and 211). For further information, please refer to 21 CFR Part 4.4(b)(2), and FDA’s January 2017 guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products.*
 - a. Please provide the supporting data, and/or summary table to demonstrate that your product conforms to the requirements under 21 CFR Part 820.*
 - b. Please provide information to demonstrate your adherence with specific regulations under the drug cGMP regulations (21 CFR Part 210 and 211).*

Updates: In the response provided in sequence 0016, the sponsor responded that they have a drug-based Quality System streamlined approach per 21 CFR Part 4.4(a)(2). Drug CGMPs are supplemented by device provisions per 21 CFR Part 4.4(b)(1).

Details on this drug-based Quality System and compliance to 21 CFR Part 4 are provided in Section 3.2.R.3 Medical Device – PFP, chapter 5 “combination product quality system information”. This section includes a summary table intended to demonstrate compliance to 21 CFR Part 4 with regard to the applicable medical device quality system elements plus a detailed description of the applied medical devices specific regulations as shown below.

Table 18 - Compliance table

Requirement	Quality system element (21 CFR)	Sanofi reference and comments
Quality system	211	Sanofi's quality system policies are documented in a quality manual compliant with 211.22. Sanofi's quality manual presents current good manufacturing practices (CGMP) requirements applicable to all functions that support clinical and commercial production, storage, testing and distribution.
Management responsibility	820.20	Sanofi has defined quality policies and objectives. Sanofi has established the quality management system that comprises four elements, as described in the quality manual: Management responsibility, resource management, process management and measurement, analysis and improvement. Sanofi's plan for quality is through the use of an integrated quality management system represented in the document hierarchy.
Design controls	820.30	Sanofi is the design control owner and maintains the design history file (DHF). To confirm that the device constituent parts design conforms to user needs and the intended use for the device, Sanofi has performed a design validation study. Manufacturing and assembly of the PFP subassemblies is contracted out to a suitable supplier. Sanofi provides customer requirements per contract.
Purchasing controls	820.50	Sanofi has a process in place to manage purchased goods including services which includes qualification of suppliers and materials, verification of purchased materials and disposition of purchased materials.
Corrective and preventive action	820.100	Sanofi has defined policies and procedures in place for corrective and preventive actions.
Installation	820.170	Installation does not apply.
Servicing	820.200	Servicing does not apply.

The sponsor also noted that Sanofi-Aventis Germany as manufacturing entity for the PFP is operating under a drug-based quality system under 21 CFR Part 211 and in addition has obtained a full quality system certification for medical devices in compliance with the technical, quality, and regulatory requirements of ISO 13485. The response to AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 30 appears adequate.

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No

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