

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215515Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION: Approval

**NDA 215515
Addendum to Review # 1**

This addendum to the Integrated Quality Assessment (IQA) for NDA 215515 dated 5/24/2022 includes minor revisions to the Executive Summary. The Executive Summary was revised to clarify and confirm the Office of Pharmaceutical Quality (OPQ) review team recommendation that the NDA be approved.

RECOMMENDATION: Approval

NDA 215515

Review #1

Drug Product Name	Amvuttra (vutrisiran injection)
Dosage Form	Injection
Strength	25 mg/0.5 mL
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Alnylam Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Lawrence Perez	Donna Christner
Drug Product	Eric Bow	Julia Pinto
Manufacturing	Helen Ngai	Kumar Janoria
Microbiology	Peggy Kriger	Elizabeth Bearr
Biopharmaceutics	--	--
Device	Porsche Bennett (CDRH)	Alan Stevens (CDRH)
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	--	--
Environmental	--	--

Submission(s)	Document Date	Discipline(s) Affected
SD-03, Original NDA	4/14/2021	All
SD-09, Response to IR	5/28/2021	Device
SD-11, Response to IR	7/29/2021	Manufacturing

Submission(s)	Document Date	Discipline(s) Affected
SD-13, Response to IR	8/19/2021	Microbiology
SD-16, Response to IR	9/30/2021	Manufacturing
SD-17, Response to IR	10/4/2021	Microbiology
SD-23, Response to IR	11/1/2021	Drug substance
SD-24, Response to IR	11/23/2021	Drug substance
SD-25, Response to IR	11/30/3021	Drug product
SD-26, Response to IR	12/15/2021	Device
SD-27, Response to IR	1/14/2022	Device
SD-28, Labeling, Carton Container	1/21/2022	Drug product
SD-29, Response to IR	1/25/2022	Drug product
SD-33, Quality Amendment ¹	3/25/2022	Manufacturing
SD-35, Response to IR	4/27/2022	Manufacturing

¹ Major amendment for packaging/labeling site change.

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III		(b) (4)	N/A		Adequate information in NDA.
Adequate				Multiple dates	Refer to Microbiology Review for DMF review history	
N/A				N/A	Adequate information in NDA.	

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

Document	Application Number	Description
IND	139086	Development of vutrisiran.

2. CONSULTS

The device aspects of the product (syringe and needle shield) were reviewed by Porsche Bennett (CDRH/OPEQ). Her review recommends approval from a device perspective, with the following comment:

“CDRH had a meeting with the firm on 01/04/2022 to obtain clarification to the firm’s response to information requests sent 12/13/2022. CDRH inquired about non-normal data, particularly for deliverable volume device performance. The firm stated that variability in deliverable volume was due to variability between (b) (4). While the performance of the attribute maintained a C/R of 95/99% despite having outliers (variability), it is important to ensure that the root cause of variability is assessed for impact to device performance as a result of drug product fill. However, the risk is low as

the product is for HCP use only and utilizing a simplistic device. Therefore, given the firm has met specification for deliverable volume, CDRH did not determine this finding to be an approvability issue. It is unclear what impact the filling variability may have on other drug product attributes that are within CDERs remit. The decision for acceptability of variability between the filling [REDACTED] (b) (4) is thus deferred to CDER.”

The finished product specification for Amvuttra includes two attributes that could potentially be impacted by variability between [REDACTED] (b) (4), i.e., *Volume in container* per USP <697>, with a limit of not less than (NLT) [REDACTED] (b) (4) mL, and *Uniformity of dosage units* per USP <905>. Based on the results provided for deliverable volume, it is unlikely that any variability between [REDACTED] (b) (4) would adversely impact on product quality with respect to these attributes. Thus, there are no outstanding concerns from a drug perspective.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality (OPQ) The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 215515 for AMVUTTRA (vutrisiran injection). From a quality perspective, the application meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Hereditary transthyretin mediated amyloidopathy (hATTR amyloidopathy) is a rare fatal disease caused by a mutation of the gene encoding for transthyretin (TTR).

Vutrisiran is a second-generation synthetic siRNA that was developed by Alnylam as a follow-on to the applicant's Onpattro® (patisiran) injection, which was the first drug approved for treatment of polyneuropathy associated with hATTR amyloidopathy (NDA 210922, AP 8/10/2018). Patisiran was also the first siRNA approved for any indication]. Unlike patisiran, which requires a lipid nanoparticle complex formulation to ensure hepatic delivery, the sense strand in vutrisiran is conjugated with an N-acetylgalactosamine (GalNAc) derived ligand that provides for delivery to hepatocytes. Vutrisiran also differs from patisiran is that vutrisiran is administered by subcutaneous injection every three months versus slow intravenous infusion every three weeks, with pretreatment to minimize infusion-related reactions, for patisiran.

Proposed indication(s) including intended patient population	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.
Duration of treatment	Chronic
Maximum daily dose	25 mg (every three months)
Alternative methods of administration	None

B. Quality Assessment Overview

The bulk drug substance and vutrisiran injection are manufactured by conventional (b) (4), respectively. Based on the initial risk

assessment, the product was considered high risk for sterility, moderate risk for bacterial endotoxins and particulates, and low risk for the remaining critical quality attributes.

Drug Substance: Adequate

The drug substance (DS)/active pharmaceutical ingredient (API), vutrisiran is a double stranded RNA molecule covalently connected to a ligand containing three *N*-acetylgalactosamine (GalNAc) residues on the sense strand. Vutrisiran has a molecular formula of $C_{530}H_{672}F_9N_{171}Na_{43}O_{323}P_{43}S_6$ (as the sodium salt) and a molecular weight of 17,289.77 Da (as the sodium salt). Vutrisiran is manufactured by (b) (4).

Manufacture of vutrisiran involves (b) (4)

All backbone linkages (*P*-linkages) of the sense strands are phosphodiesters, except for the last two linkages which are phosphothiolates. For the antisense strand the *P*-linkages are mixed, with the first two at the 3'-end and the last two at the 5'-end being phosphothiolates and the interior linkages being phosphodiesters. Since the phosphothiolate linkages in both the sense and antisense strands of vutrisiran are racemic, the drug substance vutrisiran is a diastereomeric mixture ($2^2 + 2^4$). The structure of the individual single strands (b) (4) has been established by LC/MS, MS-MS sequencing, sodium counter-ion content, UV, FT-IR, and 1D-NMR (^1H , ^{13}C , ^{19}F and ^{31}P). The structure and physicochemical properties for the duplex drug substance vutrisiran have been established by LC/MS, T_m , sodium counter-ion content, UV, FT-IR, CD, 1D-NMR (^1H , Imino- ^1H , ^{13}C , ^{19}F and ^{31}P), DSC, and TGA. For vutrisiran the release specification and the assessment of the impurities are sufficient for the control of the quality of the drug substance. The batch analyses for the clinical batches comply with the current release specification. The drug substance is stored (b) (4)

(b) (4)

Based upon the submitted stability data for the batches of drug substance manufactured by (b) (4), a retest period of (b) (4) months when stored at the recommended storage condition of (b) (4) can be granted.

Drug Product: Adequate

The proposed product is a 50 mg/mL sterile solution of vutrisiran in pH 7 (b) (4). The intended dose is 25 mg administered by subcutaneous injection every three months. The drug product contains the following USP/NF

grade excipients: sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, and sodium chloride in water for injection, with phosphoric acid and sodium hydroxide used as pH adjustors. The commercial container closure system is a prefilled syringe with a 1 mL glass barrel and (b) (4) rubber stopper plunger, filled with 0.5 mL of drug product. Adequate data supporting the use of the container closure system has been provided. The prefilled syringe configuration was used in open-label clinical safety studies and replaced an earlier vial/stopper configuration.

The applicant provided release data for twelve batches, five of which were higher strength used during development. Seven batches of 50 mg/mL drug product were submitted, three of which are registration batches for the submission. All certificates of analysis provided meet the acceptance criteria for all tested parameters, and the specifications are adequate.

Stability data for the registration batches was provided up to 18 months, with 24 months of data from supportive data provided as well. However, only nine of months of long-term leachable stability data was provided. Extractable and leachable studies have demonstrated a low risk of leachables from the container closure system. and the applicant has committed to submitting additional data as it becomes available up to 36 months. Given the available data, the applicant's commitment to continue leachable studies, and the low risk of leachables, an expiration dating period of **24 months for product stored at 2°C to 30°C** may be granted.

Labeling: Adequate

The proposed prescribing information and container labels are adequate from a product quality perspective.

Manufacturing: Adequate

The overall manufacturing process includes: (b) (4)

(b) (4)

The overall manufacturing process flow chart appropriately identifies the key process steps, inputs to each process step as well as the in-process controls. Registration batches were manufactured at approximately (b) (4) scale, which is the same as proposed for commercial manufacture.

During the manufacturing review, it was noted that the target fill volume for the syringes is (b) (4) mL with in-process control action limits of (b) (4) mL. The target fill action limits exceed the USP <1151> recommended excess fill volumes. The clinical review team was notified of the excess fill volumes and issued an IR to the applicant for additional safety analyses on 9/23/2021. The clinical reviewer has evaluated the IR response received on 10/6/2021 and determined that the excess volume does not adversely impact on safety. Thus, the applicant will not be asked to reduce the excess.

Based on the information provided in the original submission and in response to information requests, the proposed commercial manufacturing process and in-process controls are deemed adequate to ensure product quality and patient safety.

All facilities that will be used for commercial manufacture and testing of vutrisiran and Vutrisiran Injection were evaluated and deemed acceptable.

Microbiology: Adequate

The drug product is a sterile aqueous solution for IV administration. The drug product is (b) (4). Based on the information provided in the original submission and in response to information requests, the environmental controls, sterilization processes, and in-process controls are adequate to ensure sterility. The drug product specification includes appropriate test methods and acceptance criteria, per USP requirements, for sterility and bacterial endotoxins testing. All test methods are validated.

Bulk drug solution is subjected to (b) (4)

Environmental: Adequate

The Applicant submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of 'no extraordinary circumstances' was included. The claim is appropriate for the estimated amount of drug to be produced for direct use.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Sterility	Formulation, container closure, process parameters, scale, equipment, site	High	(b) (4)	Adequate	
Endotoxin/pyrogen	Formulation, container closure, process parameters, scale, equipment, site	Moderate		Adequate	
Assay/stability	Formulation, container closure, raw materials, process parameters, scale, equipment, site	Low		Adequate	
Uniformity of Dosage Units/Deliverable Volume	Formulation, container closure, process parameters, scale, equipment, site	Low		Adequate	
Osmolality	Formulation, container closure, process parameters, scale, equipment, site	Low		Adequate	
pH (high)	Formulation, container closure, raw materials, process parameters, scale, equipment, site	Low		Adequate	
Particulate Matter	Formulation, container closure, raw materials, process parameters, scale, equipment, site	Moderate		Adequate	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Leachable/extractables	Formulation, container closure, raw materials, process parameters, scale, equipment, site	Low	(b) (4)	Adequate	Applicant will continue leachables study through 36 months and report data.
Appearance	Formulation, container closure, raw materials, process parameters, scale, equipment, site	Low		Adequate	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

Senior Product Quality Assessor for Neurology Products
Office of New Drug Products

6/2/2022



Martha
Heimann

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Comments: This corrected Executive Summary for NDA 215515 contains minor edits to clarify and confirm that the OPQ review team recommends approval of the application.

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Y	
Established name(s)	Y	
Route(s) of administration	Y	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Y	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Y	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Y	
Dosage form(s) and route(s) of administration	Y	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Y	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Y	
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.	Y	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Statement of being sterile (if applicable)	Y	
Pharmacological/ therapeutic class	Y	
Chemical name, structural formula, molecular weight	Y	
If radioactive, statement of important nuclear characteristics.	n/a	
Other important chemical or physical properties (such as pKa or pH)	Y	

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Y	
Strength(s) in metric system	Y	
Available units (e.g., bottles of 100 tablets)	Y	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Y	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Y	

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	n/a	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Y	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	
Include information about child-resistant packaging	n/a	

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 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)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Y	

2.0 PATIENT LABELING

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

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

Tray Lid Labeling

(b) (4)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)		
Dosage strength		
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		
Net contents (e.g. tablet count)		
"Rx only" displayed on the principal display		
NDC number		
Lot number and expiration date		
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)		
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Y	
Medication Guide (if applicable)	n/a	
No text on Ferrule and Cap over seal	Y	
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.	n/a	
And others, if space is available	n/a	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

n/a

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Eric Bow PhD

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Julia Pinto PhD*



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CHAPTER VII: MICROBIOLOGY

Product Information	Type 1 New Molecular Entity, combination product type 2, orphan designation, rare disease indication
NDA Number	215515
Assessment Cycle Number	1
Drug Product Name/ Strength	Proprietary: AMVUTTRA; Non-proprietary: Vutrisiran/25 mg/0.5 mL, in a 1 mL prefilled syringe assembled in a passive needle safety system, single dose
Route of Administration	Subcutaneous
Applicant Name	Alynham Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Other Neuromuscular Disorders/DN1
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

(b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0003 (3)	4/14/2021
0013 (13)	8/19/2021
0017 (17)	10/4/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission was assigned to the reviewer 4/19/21 and is in the eCTD format. Amendments dated 5/5/21 (4), 5/7/21 (5), 5/20/21 (7), 5/24/21 (8), 6/29/21 (10), 7/29/21 (11), 9/8/21 (14), 10/6/21 (18), 10/27/21 (21), and 10/29/21 (22) were Information Request (IR) responses to Clinical/ Biometrics/ HF IRs, or clinical updates 8/12/21 (12). Amendments from 5/28/21 (9), 9/30/21 (16), 11/1/21 (23), 11/23/21 (24), and 11/30/21 (25) were Quality IR responses. The 8/19/21 amendment is the response to an IR from Microbiology issued to the Applicant on 7/22/21. The 10/4/21 amendment is the response to an IR

from Microbiology issued on 9/20/21. The most recent deficiencies are in italics. Some tables were copied from the submission.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

DMF ^{(b) (4)} (Type III, ^{(b) (4)}) is referenced for the depyrogenation and sterilization of the container closure components. An LOA, dated January 14, 2019, is provided. Relevant information was reviewed in D ^{(b) (4)} M88R01.docx, dated 11/17/21, adequate; D ^{(b) (4)} M84R01.docx, dated 8/12/21, adequate; D ^{(b) (4)} M81R01.docx, dated 5/27/21, adequate (summary of previous reviews); D ^{(b) (4)} M79R01.docx, dated 12/18/20, adequate; D ^{(b) (4)} M72R01.docx, dated 5/28/20, adequate.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product** – Sterile, clear, colorless to yellow solution, 25 mg/0.5 mL, pH ^{(b) (4)}, in a single dose prefilled syringe (PFS). The drug product is a chemically modified double-stranded small interfering ribonucleic acid (siRNA) that is covalently linked to a ligand containing three *N*-acetyl galactosamine residues.
- **Drug product composition** –

Ingredient	Content per syringe (mg)	Function
	50 mg/mL*	
Vutrisiran sodium	25 mg	Active ingredient
Sodium phosphate monobasic dihydrate	0.2	^{(b) (4)}
Sodium phosphate dibasic dihydrate	0.7	
Sodium chloride	3.2	
Water for Injection	q.s.	Diluent
Phosphoric acid	q.s.	pH adjustment
Sodium hydroxide	q.s.	pH adjustment

*A concentration of 50 mg/mL free acid is equivalent to 53 mg/mL in sodium salt.

- **Description of container closure system** –

Configuration	Component	Description	Manufacturer
50 mg/mL filled as 25 mg/0.5 mL	Syringe barrel	^{(b) (4)}	^{(b) (4)}
	Piston/ Plunger stopper		

Each prefilled syringe container system consists of a glass barrel with a staked needle protected with a Rigid Needle Shield (RNS), plunger stopper, and passive needle safety system. See section P.7 for other information.

Assessment: Adequate

**P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES**

(b) (4)

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Elizabeth
Barr

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Peggy
Kriger

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MARTHA R HEIMANN
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