CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 213978
Assessment # 1

Drug Product Name	Varenicline nasal spray
Dosage Form	Nasal spray
Strength	0.6 mg/mL
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Oyster Point Pharma, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Dec 17, 2020	All disciplines
Quality Amendment	Jan 29, 2021	Facility
Quality Amendment	Feb 5, 2021	Facility
Quality Amendment	Mar 15, 2021	Drug product
Quality Amendment	May 4, 2021	Manufacturing process
Quality Amendment	May 28, 2021	All disciplines
Quality Amendment	Jun 9, 2021	Quality microbiology
Quality Amendment	Jun 16, 2021	All disciplines
Quality Amendment	Jun 23, 2021	Quality microbiology
Quality Amendment	Jul 1, 2021	Manufacturing process and drug product
Quality Amendment	Jul 20, 2021	Quality microbiology
Quality Amendment	Jul 22, 2021	Drug product
Quality Amendment	Jul 27, 2021	CDRH
Quality Amendment	Jul 28, 2021	Drug product
Quality Amendment	Aug 6, 2021	Drug product
Quality Amendment	Aug 25, 2021	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor

Drug Substance	Zhengfu Wang	Suong Tran
Drug Product	Anne Marie Russell	Danae Christodoulou
Manufacturing	Carl Lee	Rose Xu
Microbiology	Daniel Schu	Yeissa ChabrierRosello
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	Cynthia Sommers	
Environmental	Anne Marie Russell	Danae Christodoulou

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	02/03/2021	Reviewed by Deborah Johnson
	III			Adequate	NA	
	III			Adequate	02/01/2018	Reviewed by Daneli López Pérez
	III			Not reviewed, information provided in the NDA submission		

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

Document	Application Number	Description
IND	138645	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	8/3/2021	Aling Dong
CDRH	Complete	Adequate with PMC # 4139-1	7/15/2021 and 8/20/2021	Kathleen Fitzgerald and Alan Stevens
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 213978, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Varenicline nasal spray, 0.6 mg/mL. All information requests and review issues have been addressed.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 8/11/2021.

Therefore, NDA 213978 is recommended for approval from Product Quality perspective with Post Marketing Commitments (PMCs).

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following PMCs have been concurred by the applicant on Aug 25, 2021 and should be included in the Action Letter:

1. *Post Marketing Commitment # 4139-1: Provide a release test method and verification data for actuation force. Final protocol submission date: Dec 27, 2021; study completion: Feb 27, 2022; and final report submission: Apr 27, 2022.*
2. *Post Marketing Commitment # 4139-2: Develop and validate a new analytical method that is sufficiently sensitive to measure* (b) (4) *in the drug product at the Acceptable Intake (AI) limits in the FDA guidance. Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) range are needed to meet the low AI recommended for* (b) (4)*. The* (b) (4) *should include those identified in the submitted* (b) (4) *Risk Assessment (*(b) (4)*) and those in the FDA guidance (*(b) (4)*). Submit data from confirmatory testing using the new method. Confirmatory testing should include aged samples of the three drug product registration lots. Propose a* (b) (4) *control strategy for your commercial drug product quality program based on the results of confirmatory testing. This may include routine release and stability testing for* (b) (4) *until sufficient data are available to support discontinuation. Submit new method, data and* (b) (4) *control strategy in a Prior-Approval supplement. Final protocol submission date: Sep 27, 2021; study completion: Dec 27, 2021; and final report submission: Jan 27, 2022.*

3. *Post Marketing Commitment # 4139-3: Improve Pump Delivery (PD) and Delivered Dose Uniformity (DDU) performance in varenicline nasal spray to meet FDA1 and USP2 guidelines. This includes determining the root cause of low dose failures, reported in release, stability, dosing orientation and freeze/thaw studies submitted in your NDA, and implementing corrective actions to your analytical methods or container closure system. Depending on the root cause, additional one-time studies such as In-Use Testing may be needed to demonstrate PD and DDU performance through end of life of the unit (15 days/60 doses) at expiry. We note that the manufacturer's Certificate of Analysis for your model pump (CPS) specifies a dose volume acceptance criteria of mean (b) (4)% and single values (b) (4)%, which do not meet FDA guidelines for pump delivery. We also note that your actuation method, (b) (4) (b) (4), also does not meet guidelines for PD and DDU performance. Submit PD and DDU method validation studies and data from confirmatory testing which meet guidelines. Confirmatory testing should include aged samples of the three drug product registration lots. Submit method validations, additional studies and data in a Prior-Approval supplement. ([1]Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation" (2002). [2]USP <601> Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers.) Final protocol submission date: Dec 27, 2021; study completion: Feb 27, 2022; and final report submission: Apr 27, 2022.*

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Varenicline nasal spray, 0.6 mg/mL is an aqueous, non-sterile, (b) (4), multi-dose, nasal spray solution packaged in 3.5 mL amber glass Type I bottles (b) (4) mL brimful capacity) with (b) (4) mL fill volume with a multidose Aptar CPS nasal spray pump. Each 50 µL spray delivers 30 µg of varenicline. The drug product is regulated as a drug device combination product.

Proposed Indication(s) including Intended Patient Population	For the treatment of dry eyes
Duration of Treatment	Instill one spray of 50 µL into each nostril twice daily (approximately 12 hours apart).
Maximum Daily Dose	0.12 mg (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Varenicline tartrate is a synthetic small molecule and a white to off-white to slightly yellow powder. The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) which was found adequate by Dr. Deborah Johnson on 2/3/2021. The applicant's specification includes a limit of (b) (4) ppm for (b) (4), a (b) (4) process impurity, which was found by OGD/Division of Clinical Review to be acceptable in DMF (b) (4) for all referencing applications based on a lifetime exposure as per ICH M7. The proposed limit was found acceptable by the Division of Ophthalmology P/T review team on Aug 3, 2021.

Drug Product: Adequate

Varenicline nasal spray, 0.6 mg/mL is an aqueous, non-sterile, (b) (4), multi-dose, nasal spray solution. All the excipients are compendial.

The revised drug product specifications are acceptable with PMCs and include the following quality attributes: appearance, ID, pH, osmolality, assay, impurities, pump delivery (PD), delivered dose uniformity (DDU), spray pattern, droplet size distribution, actuation force, sterility and net contents. The acceptance criteria for pump delivery (mean (b) (4)%) and delivered dose uniformity (mean (b) (4)%) do not meet FDA guidance for nasal spray and USP <601>. We consulted with Dr. Wiley Chambers and he indicated that the clinical division had no objection of an (b) (4)% specification. Post Marketing Commitment (PMC # 4139-3) was proposed and concurred by the applicant to improve pump delivery and delivered dose uniformity with validated methods to conform to FDA guidance on Aug 25, 2021. The applicant included the actuation force in the drug product specifications per CDRH reviewer Dr. Alan Stevens' request, however, the release test method for actuation force is not provided and the applicant agreed to submit it on Apr 27, 2021 (PMC #4139-1). All the other acceptance criteria are acceptable. The four analytical methods for pump performance (Pump Delivery, Delivered Dose Uniformity, Spray Pattern and Droplet Size Distribution) are critical analytical methods by using new test equipment for pump actuation (b) (4). A Method Verification Request (MVR) for these pump performance procedures has been sent to Office of Testing and Research (OTR) and should be reviewed post approval. The applicant identified eight possible (b) (4) leachables (b) (4) (b) (4) in the risk assessment. The Office of Testing and Research (OTR) was consulted to test drug product samples of the three registration batches #200023, 200024 and 200025 for (b) (4) using OTR qualified methods. The test results indicate that no (b) (4) were detected above the LOQ ((b) (4) ppm) in the samples dated Aug 11, 2021. However, the applicant's analytical method was not

sensitive enough to meet FDA's guidelines for (b) (4) ((b) (4) ppm), therefore, PMC# 4139-2 was requested to develop a more sensitive analytical method to monitor potential (b) (4) leachables. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in ICH Q3D guidance. CoAs for one phase 3 clinical batch stored in (b) (4) glass bottles and three primary stability batches in (b) (4) glass bottles are provided.

The commercial container closure for varenicline nasal spray consists of a 3.5 mL USP Type I amber glass (b) (4) bottle (b) (4) mL brimful capacity) from and a Snap-On 50 µL Cartridge Pump System (CPS) (b) (4) (b) (4) multidose nasal spray pump with a blue colored protective cap and a white clip. Aptar CPS nasal spray pump is referenced in DMF (b) (4) and also provided in the NDA submission. CDRH assessed biocompatibility of non-drug contacting components and found it acceptable by Dr. Kathleen Fitzgerald on 7/15/2021. Additionally, Dr. Alan Stevens from CDRH reviewed the device performance data including pump activation force, pump delivery volume and the device EPR Control Strategy and found it adequate with one PMC (PMC# 4139-1) on 8/20/2021.

The applicant has submitted 12 months stability data at long term (25°C/60%RH) and intermediate (30°C/65%RH) storage conditions and 6 months at accelerated condition (40°C/75%RH) for the three registration batches (#20023, 20024 and 20025) of varenicline nasal spray, 0.6 mg/mL in (b) (4) glass bottles. Low dose failures are reported in Pump Delivery and Delivered Dose Uniformity stability test results. PMC #4139-3 was proposed to address this concern. All the other quality attributes met the specifications. The product is not stable during the freeze-thaw study and one caution statement of "Do not freeze" is proposed in the labeling. Therefore, the expiration date of 12 months is granted when stored at 20 °C- 25 °C.

The storage statement is "Store at 20°C-25°C (68°F-77°F). Do not freeze." and will be finalized at the OND's labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The process involves formulating Varenicline nasal spray in a (b) (4) (b) (4) (b) (4) (b) (4) All the facilities

associated with the application appear acceptable to support the manufacture of Varenicline nasal spray, 0.6 mg/mL. No Pre-Approval Inspections are recommended during this review cycle.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

Varenicline nasal spray, 0.6 mg/mL will not be labeled as a sterile product. However, it will be manufactured using an (b) (4) and sterility testing (USP <71>) will be conducted on the product at the time of release and on stability to ensure the ability of the drug product to maintain its microbiological quality across the proposed shelf life. This application is recommended for approval on the basis of product quality microbiology.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure Raw materials	L	(b) (4)	L	
(b) (4) impurities	• Formulation • Container closure[1] • Process parameters • Scale/equipment	H		M	
pH	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	
Pump Delivery And Delivered Dose Uniformity	• Formulation • Container closure	H		H	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Aug 27, 2021

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213978
Assessment Cycle Number	1
Drug Product Name/ Strength	Varenicline tartrate; (b) (4) mg/mL ((b) (4) µg/spray (0.05 mL))
Route of Administration	Intranasal
Applicant Name	Oyster Point Pharma Inc.
Therapeutic Classification/ OND Division	Cholinergic agonist/Division of Ophthalmology
Manufacturing Site	(b) (4)
Method of Sterilization	N/A. The drug product is non-sterile.

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001	**12/17/2020**
Seq 0003	**01/29/2021**
Seq 0011	**05/24/2021**
Seq 0012	**05/28/2021**
Seq 0014	**06/09/2021**
Seq 0015	**06/16/2021**
Seq 0016	**06/23/2021**
Seq 0020	**07/20/2021**
Seq 0023	**07/27/2021**

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

Remarks: The subject drug product is indicated to treat dry eye disease. The subject drug product is an aqueous, non-sterile, (b) (4), multi-dose, nasal spray solution. The formulated bulk solution is filled into 3.5 mL Type I (b) (4) amber glass bottles with a multidose nasal spray pump (b) (4) (b) (4) It is noted that this container-closure system is to (b) (4) (b) (4), that have been shown to induce nasal epithelium

toxicity." A similar container-closure system is currently approved for use with (b) (4) (NDA (b) (4)).

Note that the subject drug product is labeled as non-sterile; however, it has a test procedure and acceptance criterion for evaluation of sterility at release and stability (See Section P.5 for further details).

Deficiencies were conveyed to the applicant in an Information Request, dated 10 May 2021. The applicant submitted informal responses via email to the 10 May 2021 IR on 11 May 2021 to facilitate discussions for a 12 May 2021 T-con with the applicant. The informal response included: (b) (4)

(b) (4)

The reviewer participated in a 12 May 2021 T-con with the applicant, which included 1) discussion with the clinical division regarding the proposed strength of the drug product to be marketed and 2) discussion regarding the product quality microbiology deficiencies conveyed in the 10 May 2021 Information Request. The reviewer noted the following major concerns with the application from a product quality microbiology perspective:

(b) (4)

(b) (4)

The 24 May 2021 amendment (Seq 0011) was a response to the 10 May 2021 Information Request. The amendment includes a commitment to provide (b) (4) (b) (4) (b) (4) The applicant states that both studies will be performed with aged components to support the proposed shelf life of (b) (4) (b) (4)

The 28 May 2021 amendment (Seq 0012) referenced the 12 May 2021 T-con with the Agency and included updated labeling, information for the inclusion of the low dose formulation (0.6 mg/mL) of the subject drug product, updated product quality attributes, and updated specifications (b) (4) (b) (4) It was noted that updated Section 3.2.P.1 of the amendment indicated (b) (4) (b) (4)

A deficiency was conveyed to the applicant in a 14 June 2021 Information Request for clarification on the proposed strengths of the drug product to be marketed. The 16 June 2021 amendment (Seq 0015) confirmed that (b) (4) the 0.6 mg/mL strength of the drug product is the proposed commercial strength. Additionally, a deficiency was conveyed to the applicant in a 21 June 2021 Information Request for clarification (b) (4) (b) (4) The 23 June 2021 amendment (Seq 0016) confirmed the drug product will not be labeled as a sterile product. (b) (4) (b) (4)

(b) (4)

The submission is **recommended** for approval on the basis of product quality microbiology.

Concise Description of Outstanding Issues: N/A.

Supporting Documents:

- Microbiology Review of NDA (b) (4) dated 25 October 2016, for a review of the (b) (4)

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – Non-emergency Use Nasal Spray

Date	7/13/2021
To:	Kelly Ballard
Requesting Center/Office	CDER/OPQ
From	Kathleen Fitzgerald OPEQ/OHT3/DHT3C
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C
Through (Division) ***Optional**	Rumi Young, Assistant Director OPEQ/OHT3/DHT3C
Subject:	ICC2100124 NDA213978 Oyster Point Inc. Varenicline Tartrate Indications for Use: Dry eye disease.
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies
	Comments to Review Team: None
	PMC/PMR or CR Deficiencies: None

Digital Signature Concurrence Table		
Reviewer	**Team Lead**	**Division (Optional)**

1. PURPOSE

This Nasal Spray review will cover the following review areas:

☒ Biocompatibility of non-drug contacting components

This review will not cover the following review areas:

☒ Nasal Spray performance per CDER guidance[1]
☒ CDRH Quality Systems Assessment / Facilities*
☒ Drug product/container closure performance
☒ Biocompatibility drug contacting components
☒ Sterility
☒ Human factors
☒ Control Strategy

*It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

2.1. Picture of Final Device Presentation

Figure 3: Drawing of Aptar Cartridge Pump System (CPS) Nasal Spray Pump and Materials of Construction

(b) (4)

(b) (4)

Figure 4: **Aptar Cartridge Pump System (CPS) Nasal Spray Pump- Air and Liquid Flow**

2.2. Design Requirements

Syringe Description

Requirement	Describe
Intended user	Home use, Self-administration for patients 17 years and older. For intranasal use only.
Dosing regiment	Twice daily (approximately 12 hours apart). For intranasal use only.
Dose	One spray per nostril.

3. DEVICE CONSTITUENT REVIEW

Nasal Spray materials

CPS Component	Contact Material – Chemical Description	Current Material Trade Name/Manufacturer or Supplier
(b) (4)		

CPS Component	Contact Material - Chemical Description	Material Trade Name/Manufacturer or Supplier
(b) (4)		

CPS Component	Contact Material - Chemical Description	Material Trade Name/Manufacturer or Supplier
		(b) (4)

CPS Component	Contact Material - Chemical Description	Material Trade Name/Manufacturer or Supplier
		(b) (4)

Table 2: Aptar CPS Nasal Spray Pump Components and Material of Construction

CPS Pump Component	Material of Construction- Chemical Description	Product Contact
(b) (4)		

Relevant information is provided in DMF (b) (4) in:

(b) (4)

4.3.4. Biological Reactivity Tests for Aptar CPS Pump

Aptar has evaluated all plastic materials of critical components which are in contact with the drug product and /or patient mucosa of the [redacted] CPS pumps according to Biological reactivity tests:

Biological reactivity test, In Vitro / Biological evaluation of medical devices

USP <87> / ISO 10993 Part 5 Tests for in vitro cytotoxicity. Cytotoxicity Study Using the USP and ISO Elution Method

Biological reactivity test, In Vivo / Biological evaluation of medical devices

USP <88> / ISO 10993 Part 11; Tests for systemic toxicity Systemic Toxicity Study in Mice (extracts: SC, AS, PEG, SO)

USP <88> / ISO 10993 Part 10; Tests for irritation and skin sensitization Intracutaneous Irritation Study in Rabbits [redacted]

USP <88> USP Muscle Implantation Study in the Rabbit (5 days)

[redacted] classification -> Results of test 2.1 - 2.3

ISO 10993 Part 10 Tests for irritation and skin sensitization ISO Guinea Pig Maximization Sensitization Test [redacted]

Reports from these studies are part of Aptar Radolfzell GmbH's US Type III DMF # [redacted] in module 3.2.P.5.1 Safety Data for materials and components. All materials passed the tests for the material testing type according to tests described above.

Table 1. Biocompatibility Review of NO drug/fluid path contact parts-Prolonged use

Component	Contact Classification	Endpoints	Method	Result (Pass/Fail)
Cap: [redacted]	Intact Skin contact	Cytotoxicity Acute Systemic Toxicity Study Irritation and skin Sensitization testing	ISO 10993-5 USP <88> / ISO 10993-11) ISO 10993-10	Pass
[redacted]	None-No patient contact	N/A	N/A	
Finger Flange: [redacted]	Intact Skin contact	Cytotoxicity Acute Systemic Toxicity Study Irritation and skin Sensitization testing	ISO 10993-5 USP <88> / ISO 10993-11) ISO 10993-10	Pass
Fixture: [redacted]	None-No patient contact	N/A	N/A	
Clip: [redacted]	Intact Skin contact	Cytotoxicity Acute Systemic Toxicity Study Irritation and skin Sensitization testing	ISO 10993-5 USP <88> / ISO 10993-11) ISO 10993-10	Pass
Nasal actuator-external part: [redacted]	Nasal mucosa	Cytotoxicity Acute Systemic Toxicity Study	ISO 10993-5 USP <88> / ISO 10993-11)	Pass

		Irritation and skin Sensitization testing Implantation	ISO 10993-10	

Reviewer Comments

- LOA is present in NDA 213978 to reference DMF (b) (4) for the Aptar Nasal spray. Section 3.2.P.5.1 of DMF (b) (4) has material and biocompatibility information. The materials/manufacturing, (b) (4) prior to testing and biocompatibility testing for the Aptar Nasal spray are identical unchanged from previously approved container closure combination products. The biocompatibility information of the non-drug contacting components is adequate with acceptable test results.

<<END OF REVIEW>>

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – Non-emergency Use Nasal Spray

Date	8/20/2021
To:	Kelly Ballard
Requesting Center/Office	CDER/OPQ
From	CAPT Alan Stevens Assistant Director Injection Devices Team OPEQ/OHT3/DHT3C
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C
Subject:	Amended Review – This review amends CDRH's July 13, 2021 review memo. ICCR Case 00058823 ICC2100124 NDA213978 Oyster Point Inc. Varenicline Tartrate Indications for Use: Dry eye disease
Recommendation	**Final Recommendation:** ☐ Device Constituent Parts of the Combination Product are Approvable. ☑ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies
	Comments to Review Team: None
	PMC/PMR or CR Deficiencies: Provide a release test method and verification data for activation force.

Digital Signature Concurrence Table		
Reviewer	**Team Lead**	**Division (Optional)**

1. PURPOSE

This review is amending the CDRH review provided on July 13, 2021 in order to provide review of the device performance data.

This Nasal Spray review will cover the following review areas:

☒ Nasal Spray performance per CDER guidance for the following endpoints:
- Pump activation force
- Pump delivery volume

CDER confirmed coverage of other device performance endpoints from FDA guidance, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products--Chemistry, Manufacturing, and Controls Documentation*

☒ Device EPR Control Strategy

This review will not cover the following review areas:

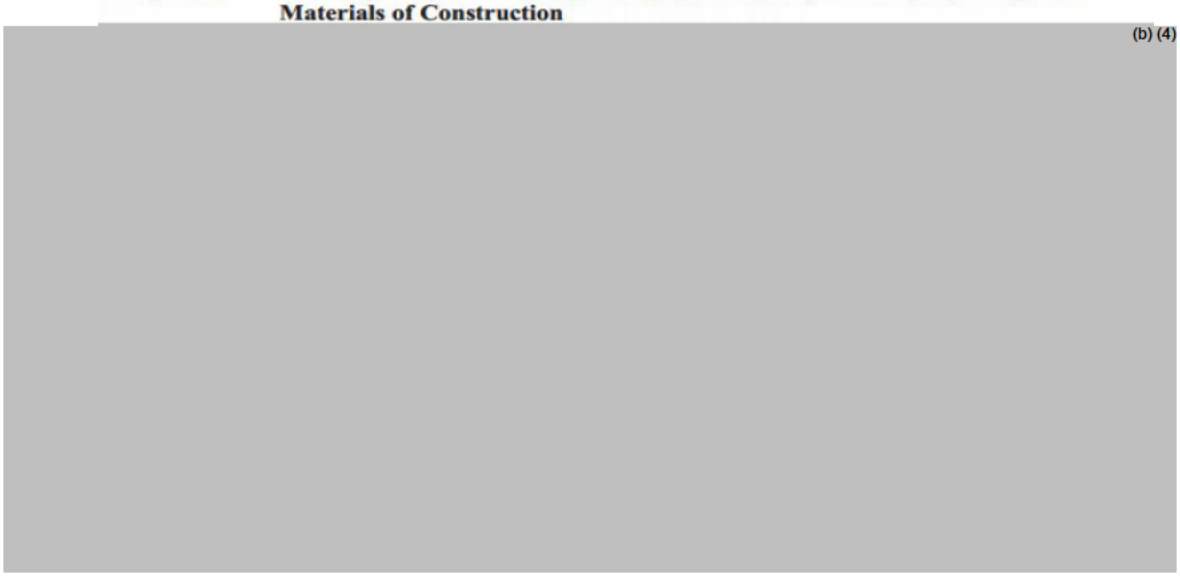
☒ Biocompatibility of non-drug contacting components (Biocompatibility is already covered for this device in CDRH, July 13, 2021 Review memo)
☒ CDRH Quality Systems Assessment / Facilities*
☒ Drug product/container closure performance
☒ Biocompatibility drug contacting components
☒ Sterility
☒ Human factors

*It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[1]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

2.1. Picture of Final Device Presentation

Figure 3: Drawing of Aptar Cartridge Pump System (CPS) Nasal Spray Pump and Materials of Construction



[1] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Figure 4: Aptar Cartridge Pump System (CPS) Nasal Spray Pump- Air and Liquid Flow

2.2. Design Requirements

Syringe Description

Requirement	Describe
Intended user	Home use, Self-administration for patients 17 years and older. For intranasal use only.
Dosing regiment	Twice daily (approximately 12 hours apart). For intranasal use only.
Dose	One spray per nostril.

3. PERFORMANCE SPECIFICATIONS

The device performance specifications are located in Module 3.2.P.4 and 3.2.P.7:

Note that the sponsor modified the Activation Force in their August 6, 2021 IR response. The original specification was activation force (b) (4) N. The modified specification is activation force (b) (4) N.

Table 3: Specifications of Aptar Cartridge Pump System (CPS) 50 µL Nasal Spray Pump (with (b) (4))

Characteristic	Description	Specification	Aptar test method
Priming	(b) (4)		
Dose volume			
Droplet size distribution			
Spray Pattern			
Dip tube length			

Review Comments

- This review covers pump delivery (inclusive of Priming and repriming) and activation force. Droplet size and spray pattern are being covered by CDER/OPQ. Dip tube length is covered as part of the assessment of total expellable doses.

- The EPR list located in 3.2.P.4 is missing activation force.

    - *Update – The July 27, 2021 IR response added activation force as EPR.*

- Table 3 (shown above) from section 3.2.P.7 describes the pump data as being tested with "aptar test medium". Design verification data should be provided with varenicline at each concentration.

    - *Update – The August 6, 2021 IR response provided pump delivery testing with each drug concentration.*

4. DEVICE PERFORMANCE DATA

I confirmed with CDER/OPQ review staff that CDRH review should assess the priming, pump delivery, total deliverable dose per container, and activation force.

Stability data are provided for three registration batches per dose (0.6 mg/mL (b) (4)).

Performance Requirement	Specification	Verification (Y/N)	Validation (Y/N)	Stability Module 3.2.P.8 (Y/N)	Shipping/ Transportation (Y/N)
Prime	(b) (4)	Y	Y	Y	Y
Reprime		Y	Y	N	N

Pump delivery (dose volume)	(b) (4)	Y	N*	Y	Y
Actuation Force		Y	Y	N	N

*The specification does not meet the FDA guidance recommendation. The manufacturer refers to clinical experience with the product. I did not review the clinical data and defer to CDER on acceptability of pump delivery specification.

- Review of stability testing provided in the manufacturer's August 6, 2021 IR response and 3.2.P.8 demonstrates a single test sample fail to meet the requirements for individual pump performance at 12 months.
- Pump delivery mean values are within specification for all stability conditions. Also, while the mean values do exhibit more variability over time, they do not appear to be trending in any specific direction.
- Pump design verification testing included in 3.2.P.2 appear to demonstrate good performance over the bottle volume. However, these appear to be time zero data delivering the aptar test media.
- The application describes use of a (b) (4) during pump delivery verification testing. The validation of this method is unknown. I reviewed the response to IR response dated, July 22, 2021, (b) (4) (b) (4)

(b) (4)

The validity of the test compensation method is also not well-described.

Conclusion –
During an August 19, 2021, team meeting, it was agreed that a PMC to address pump delivery specifications, and (b) (4) (b) (4) method validation would be provided in an approval recommendation. I concur with this approach.

5. CONTROL SPECIFICATIONS

- Activation force specification is not included in the 3.2.P.5 control specifications. Add specifications for pump activation force and describe the test method.
    - *Update based on July 27, 2021 IR response: Sponsor proposes to submit the updated 3.2.P.5.2 Pump Delivery method and 3.2.P.5.3 verification data for actuation force as a CBE-0 upon approval of the NDA.*
    - *Following August 19, 2021 discussion with CDER, I recommend adding PMC to approval of NDA 213978 to request method validation for activation force release test.*

- Pump delivery specifications include tier specifications that fall outside (b) (4)%. Provide justification for allowing lots with product failing to meet the (b) (4)% pump delivered volume specification.
    - CDER updated me on July 21, 2021, stating they issued IR requesting manufacturer to revise these specifications.
    - I requested clarification from CDER on August 18, 2021 and was provided the following response:
    - *In the July 22, 2021 IR response, Manufacturer revised the pump delivery specification to the following:*
        - *(a) Mean (n=(b) (4)): (% Target Weight) value must be within (b) (4)% Target Weight ((b) (4) mg - (b) (4) mg)*
        - *(b) No individual spray may be outside (b) (4)% Target Weight ((b) (4) mg – (b) (4) mg)*
    - *Following August 19, 2021 team meeting, CDER will be adding PMC for the (b) (4) method validation and pump delivery specification improvement. I concur this will address the performance issues observed in my review.*

Conclusion

Sponsor proposes to submit the updated 3.2.P.5.2 Pump Delivery method and 3.2.P.5.3 verification data for actuation force as a CBE-0 upon approval of the NDA. I discussed with CDER during August 19, 2021 team meeting and will recommend this be added as PMC.

6. INFORMATION REQUESTS

(b) (4)

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

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

/s/

CHUNCHUN N ZHANG
08/27/2021 08:10:00 AM