

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215352Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 215352 Assessment # 2

Drug Product Name	MydCombi (Tropicamide /Phenylephrine Hydrochloride Ophthalmic Spray), 1%/2.5%
Dosage Form	Ophthalmic spray
Strength	1%/2.5%
Route of Administration	Topical ophthalmic spray
Rx/OTC Dispensed	Rx
Applicant	Eyenovia, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	Nov 9, 2022	All disciplines
Quality Amendment	Jan 6, 2023	Drug product
Quality Amendment	Feb 6, 2023	Quality microbiology
Quality Amendment	Feb 10, 2023	CDRH
Quality Amendment	Feb 28, 2023	Quality microbiology
Quality Amendment	Mar 7, 2023	CDRH
Quality Amendment	Mar 17, 2023	Manufacturing process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Daniel Jansen	Suong Tran
Drug Product	Elise Luong	Chunchun Zhang
Manufacturing process and facilities	Jing Fang	Tianhong Zhou
Microbiology	Catherine Gilbert	Yan Zheng
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Shazma Aftab	
Application Technical Lead	Chunchun Zhang	



QUALITY ASSESSMENT



Laboratory (OTR)	NA	
Environmental	Elise Luong	Chunchun Zhang

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)	(b) (4)	Adequate	6/9/2021	Reviewed by Daniel Jansen
	II			Adequate	12/31/2018	Reviewed by Yun Wang
	III			Not reviewed, information provided in the NDA submission		
	III			Not reviewed, information provided in the NDA submission		
	V			Not reviewed, information provided in the NDA submission		

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

Document	Application Number	Description
IND	135936	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH (ICCR# 00881223)	Complete	adequate	3/20/2023	Keith Christopher
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 215352 was recommended for complete response from quality microbiology, facilities and CDRH perspective during the original submission review on 10/22/2021. Refer to IQA #1.

Both drug substance, drug product and manufacturing process disciplines uphold an approval recommendation for this class-2 resubmission. Quality microbiology has found all the identified deficiencies have been adequately addressed.

The compliance status of the device assembly manufacturing facility, Eyenovia (FEI# 3015097092) was determined acceptable based on the most recent inspection performed ending Apr 5, 2023. Therefore, OPMA issued an overall recommendation of "approval" on May 1, 2023. CDRH review team has found all the previous deficiencies are resolved in the consult memo dated on 3/20/2023. In agreement with the above recommendation, NDA 215352 is recommended approval from Product Quality perspective.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Tropicamide /Phenylephrine Hydrochloride ophthalmic spray is a sterile, clear, colorless solution fixed-dose combination of tropicamide 1% (80 µg/8 µL) and phenylephrine Hydrochloride 2.5% (200 µg/8 µL) ophthalmic spray packaged in (b) (4) 2 mL glass vial and then enclosed into a sterile Optejet dispenser. Each metered spray delivers 8µL which contains 80 µg tropicamide and 200 µg phenylephrine Hydrochloride. Currently only Tropicamide

ophthalmic solution and Phenylephrine Hydrochloride ophthalmic solution are approved products and both have USP monographs.

Proposed Indication(s) including Intended Patient Population	For the treatment of inducing mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired
Duration of Treatment	One metered spray should be administered as required, up to a maximum of 3 sprays per eye per day
Maximum Daily Dose	Tropicamide 480µg and Phenylephrine Hydrochloride 1200µg. See the package insert for details
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Both drug substance Tropicamide and Phenylephrine Hydrochloride were reviewed during the original submission and were found adequate. No new drug substance information has been included in the resubmission. Refer to the drug substance review #1.

Drug Product: Adequate

Refer to the drug product review #1.

In this resubmission, the applicant has submitted 24 months long-term stability data for one registration batch manufactured at the commercial manufacturing site Alcamí and also provided 9 months long-term stability data for 3 process validation batches from Alcamí. All the quality attributes met the specifications. Therefore, the expiration date of 24 months is granted when stored at (b) (4) °C- 25 °C.

The storage statement is "Store at (b) (4) °C-25°C ((b) (4) °F-77°F)" " (b) (4) 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 manufacturing process includes: (b) (4). The applicant adequately responded to all identified process

deficiencies. Eyenovia (FEI# 3015097092) is found acceptable from the recent inspection. All the other facilities are acceptable based on the inspection or profile.

Biopharmaceuticals: N/A

Microbiology (if applicable): Adequate

The drug product is (b) (4) filled into vials. The outstanding issues identified in the original review have been adequately addressed.

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	
Impurities	- Formulation - Container closure - Process parameters - Scale/equipment	H		L	
pH	- Formulation - Container closure - Process parameters - Scale/equipment	L		L	
Particulate matter	- Formulation - Container closure - Process parameters - Scale/equipment	L		L	
Optejet dispenser	- Formulation - Container closure	H		L	
Sterility	- Formulation - Container closure - Process parameters - Scale/equipment	H		L	

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

Labeling comments will be communicated to OND during the labeling discussion.

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., May 1, 2023

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215352
Assessment Cycle Number	2
Drug Product Name/ Strength	Tropicamide 1%/Phenylephrine HCl 2.5% Ophthalmic Spray (MydCombi)
Route of Administration	Topical Ophthalmic Spray
Applicant Name	Eyenovia, Inc.
Therapeutic Classification/ OND Division	CDER/OSM/Division of Ophthalmology
Manufacturing Site	Alcami Corporation: (b) (4) (b) (4) FEI: (b) (4) (b) (4) (b) (4) FEI: (b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

The drug product (b) (4) filled into vials. The drug product vial is then assembled into a micro-spray device (Optejet injector cartridge) (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Resubmission (24)	11/08/2022
Stability IR Response (27)	01/20/2023
IR Response (29)	02/16/2023
IR Response (32)	03/09/2023

Highlight Key Issues from Last Cycle and Their Resolution: Issues regarding inadequate CCIT (b) (4)

(b) (4) were identified in the first cycle for this NDA.

Remarks: This is an eCTD submission. The original review was found inadequate and CR was recommended. A CRL was sent on 10/22/2021. A post-CRL Type A meeting was held to discuss the proposed CCIT and in-use study protocol. A meeting amendment including the updated CCIT protocol was subsequently reviewed (see supporting documents list below)

Concise Description of Outstanding Issues

(List bullet points with key information and update as needed): N/A

Supporting Documents:

- N215352MR01.docx dated 09/16/2021 for original NDA review
- N215352-20210114-MR01.docx dated 01/14/2022 and N215352-20220228-MR01.docx dated 02/23/2022 for post-CRL Type A meeting package and MP amendment review

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Unchanged, information summarized from N215352MR01.docx)

- **Description of drug product** – MydCombi (tropicamide 1% and phenylephrine HCl 2.5%), is a sterile, clear, colorless topical ophthalmic spray indicated to induce mydriasis for routine diagnostic procedures and when short term pupil dilation is desired.
- **Drug product composition** –

Ingredient	Content per mL	Function
Phenylephrine HCl, USP	2.5	API
Tropicamide, USP	1.0	API
(b) (4) ® Benzalkonium Chloride (b) (4) , USP/NF	0.01	Preservative
Hydrochloric acid, USP	q.s.	pH Adjustment
Sodium hydroxide, USP	q.s.	pH Adjustment
WFI, USP	q.s.	(b) (4)

- **Description of container closure system** –

Component	Packaging	Description (Gland material code)	Manufacturer
Vial	Primary		(b) (4)
Stopper	Primary		
Seal	Secondary		
Cartridge	Primary		
Cartridge tray	Secondary		
Base	Secondary		

(b) (4)

Note to Reviewer: Diagrams taken from the original NDA submission. (b) (4)

(b) (4)

Assessment: N/A, no change.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Memorandum

DATE: March 20, 2023

FROM:

Keith Christopher, PhD
Chemical Engineer
Glaucoma, Cornea, and Surgical Devices Team
CDRH/OPEQ/OHT1/DHT1A

TO: Record

SUBJECT: NDA 215352 (ICC2200986), Engineering Review
Eyenovia Inc.

DEVICE: Tropicamide 1%/ Phenylephrine HCl 2.5% Ophthalmic, MiDD System

CONTACT: Ms. Ginger Clasby, Vice President, Clinical and Regulatory Affairs

RECOMMENDATION: **Completed – No Deficiencies (CND)**

BACKGROUND:

Eyenovia is pursuing development of [REDACTED] (b) (4)
[REDACTED] a fixed combination formulation containing phenylephrine (PE) hydrochloride and tropicamide (Trop) to dilate the pupil (mydriasis). They are seeking feedback/evaluation for the testing information that was submitted in the latest installment in the NDA.

INDICATIONS FOR USE:

The sponsor proposes the following Indications for Use statement for their device:

Mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

REGULATORY HISTORY:

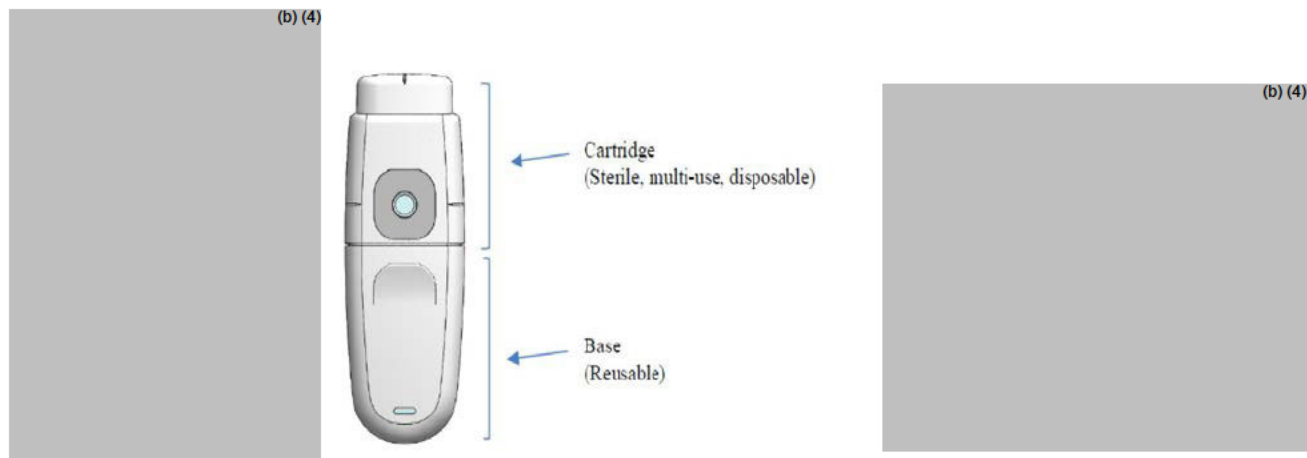
- On December 28, 2020, the Applicant submitted a New Drug Application (NDA) 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5%), Ophthalmic Spray. At the

time of this submission, the proposed product was not deemed to be a drug-device combination product.

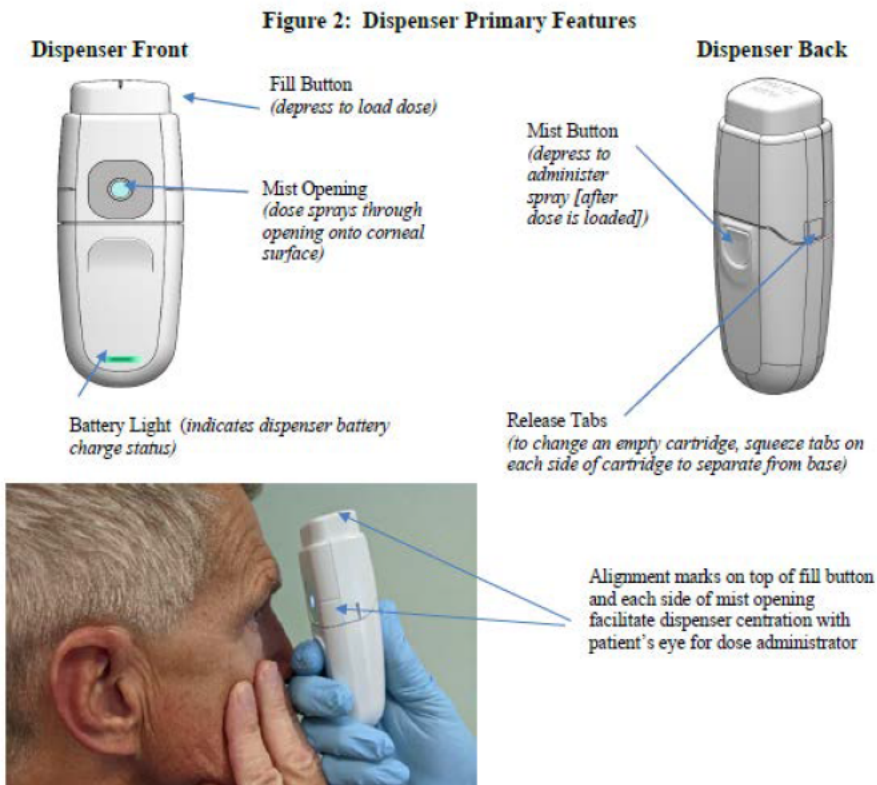
- On August 23, 2021, the Applicant submitted information for review. According to the Applicant, this was submitted in response to a June 29, 2021 request for information. During the review cycle, NDA 215352 was deemed a drug-device combination product. An engineering consult from CDRH was performed that identified high-level issues and deficiencies.
- On October 22, 2021, the Agency sent the Applicant a Complete Response (CR) letter.
- On December 28, 2022, the Applicant resubmitted their new drug application NDA 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5), Ophthalmic Spray.

DEVICE DESCRIPTION:

Eyenovia is pursuing development of (b) (4) a fixed combination formulation containing phenylephrine (PE) hydrochloride and tropicamide (Trop) to dilate the pupil (mydriasis). The dispenser used for the drug delivery - Eyenovia's Optejet® dispenser with MAP™ technology (Microdose Array Print) is a horizontal topical delivery system for the eye and works similar to an inkjet printer. Medication is administered as a directional mist in a micro droplet array, coating the corneal surface of the eye like pixels. Contact happens at low velocity minimizing ocular impact. Unlike a traditional eyedropper that uses gravity, the device dispenses medication horizontally and designed to administer every dose to the patient who could be seated or standing. The drug delivery dispenser comprised of a reusable base containing battery and electronics that is paired with a sterile, multi-use disposable cartridge containing Mydcombi (tropicamide 1% and phenylephrine HCl 2.5%) drug solution. The drug solution is sterile-filled into a (b) (4) 2mL glass vial (the primary drug container) that resides inside the cartridge; thus, the cartridge is the primary container closure system (CCS).



Key features of the dispenser are shown in Figure 2. To assemble the dispenser, the user removes the cartridge and base from the packaging, aligns the two components, then presses them together until they click into place. The user then performs a one-time priming sequence to puncture the seal of the vial (inside the cartridge) and load the drug solution into the cartridge fluid path for dosing. This priming sequence is performed by cycling through 2 steps sequentially: depress the fill button (Step 1), then depress the mist button (Step 2) until a drug dose is emitted through the mist opening.



Mechanism of Action

The dispenser mechanism of action is demonstrated in Figure 3. To administer a drug spray, the fill button on the cartridge is depressed, (b) (4)

Only a single dose can be administered at a time. To administer a second dose, the dispenser must be re-loaded (by depressing the fill button). The dispenser cartridge contains approximately 180 doses of drug solution. When drug solution is depleted, the used cartridge may be separated from the base by squeezing the cartridge release tabs. Another sterile Mydcombi cartridge may then be assembled with the reusable base.

Figure 3: Dispenser Mechanism of Action

(b) (4)



Detailed Description of Base

The non-sterile reusable base of the dispenser ([Figure 6](#)) contains a control board powered by a lithium-ion battery (charged via USB connection to the charging port), light-emitting diode (status light), and the mist (or dosing) button that is pushed to spray drug solution.

Figure 6: Base Components

(b) (4)

Specifications for Mydcombi Base and Charger

Base Specifications

Parameter	Specifications
Operating power	4.1VDC
Power source	Internally powered, Lithium-Ion Battery
Instrument make / model	Eyenovia / Mydcombi™ Base
Dimensions	50 length, 120mm height, 40mm width (When assembled with cartridge)
Weight (system)	< 100g (When assembled with cartridge)
Allowed operating temperature range	15°C to 30°C
Allowed shipping and storage temperature range	15°C to 30°C at relative humidity of 15% to 90% RH, non-condensing
Allowed operation, storage, and shipping humidity range	15°C to 30°C at relative humidity of 15% to 90% RH, non-condensing
Allowed operation, storage, and shipping atmospheric pressure	700hPa to 1060hPa
Electrical shock protection - Classification / Degree	Internally powered Class I
Battery life	2-4 weeks, if used as indicated.
(b) (4)	
Software version	Software version number can be obtained by calling the manufacturer.

Charger Specifications (Micro-USB to USB Cable with Wall Plug)

Parameter	Specifications
Type	Switching Power Supply
Input	100-240V~, 50/60 Hz 200mA
Output	5V, 1A
USB Cable Minimum Requirements	5V, 1A
USB cable must be UL Listed. Must meet US Standard Level VI energy efficiency. Must meet DOE & CEC regulatory requirements. Examples of acceptable cables include those with UL number E178074 or Homespot Model S005AYU0500100.	

ENGINEERING REVIEW:

The dispenser used for Mydcombi is Eyenovia's Optejet® dispenser, (b) (4)

Verification and validation testing presented in this section characterizes dispenser performance independent of drug product. Additional testing validating reliable delivery of the specified spray volume for Mydcombi drug solution is presented in [Section 3.2.P.2.4.6](#).

Verification and validation testing of the Mydcombi dispenser per [QD-16181 Master Verification and Validation Plan](#) was completed at Eyenovia's R&D Laboratory (Reno, NV).

The master test plan involved verification and validation testing to confirm:

- The acceptability of product packaging
- Forces required for spray administration and dispenser assembly
- The absence of ingress leakage in the fluid path of the primary CCS
- Spray volume reliability
- Electro-mechanical system functional performance

Test results demonstrated dispenser performance at Time 0 and 12 months in compliance with all established specifications and requirements.

Transit Testing:

Packaging and shipping validation studies were performed per ASTM D4169-22 requirements using sterile packaged Mydcombi cartridges subjected to climactic conditioning, package performance testing, and accelerated aging ($55 \pm 2^{\circ}\text{C}$) for 38 days (an equivalent of 12 months).

Table 12: Cartridge Packaging Validation Test Summary

Requirement	Criteria	Sample Size	Result	Outcome
Transit/Conditioning				(b) (4)
				PASS
				PASS
				PASS
				PASS
				PASS
				PASS
				PASS

Requirement	Criteria	Sample Size	Result	Outcome
(b) (4)				PASS
				PASS

Table 13: Base Packaging Validation Test Summary

Requirement	Criteria	Sample Size	Outcome
(b) (4)			PASS
			PASS

***Engineering Reviewer Comment:** The sponsor has provided transit data with testing according to the applicable and recognized standard. All evidence found in file TR-17332 and TR-17224 are acceptable for the cartridge and the base of the device. There are no deficiencies identified with the shipping validation. ACCEPTABLE*

Actuation Force Testing:

Dispenser priming, dosing, and assembly force specifications were validated via bench testing and with intended users (Section 3.2.P.7.5) as specified in QD-16181 Master Verification and Validation Plan, Section 3.11. It should be noted that these same specifications were applied to manufacture of the dispensers successfully used in the MIST-1 and MIST-2 pivotal clinical studies presented in Section 5.3.5.1. Actuation force testing performed is detailed below.

Prior to first use, the fill button on top of the cartridge must be depressed to puncture the primary drug container septum (vial loading) to allow drug solution to flow into the CCS fluid path. After vial loading, the fill button must also be depressed to load each drug dose prior to administration (priming). Twenty (20) dispensers were tested to evaluate vial loading and priming button forces. Each dispenser was positioned with the bottom against the flat surface of a calibrated force gage and the force required to depress the fill button was measured.

The priming force specification is (b) (4). Test data at Time 0 and 12 months showed priming force normally distributed and (b) (4), with > 0.9990 reliability at 95% confidence; thus, meeting specification. At 12 months, the mean force required for priming was 5.929 lb. (SD 0.4090). (Found in TR-17321 and TR-17332)

Table 14: Vial Loading/Priming Button Force Test Summary

Requirement	Criteria	Sample Size	Result ¹	Outcome
(b) (4)				PASS
				PASS

¹ Results shown are for both Time 0 and 12 months.

Engineering Reviewer Comment: The sponsor has not provided justification for the force limits. A request will be made for them to provide justification. **INFORMATION NEEDED**

To spray a dose, the mist (or dosing) button on the back of the dispenser base must be depressed. Twenty (20) cartridges were tested to evaluate mist button actuation forces. Each dispenser was positioned with the face against the flat surface of a calibrated force gauge and the force required to depress the mist button was measured.

The mist button actuation force specification is (b) (4). Test data at Time 0 and 12 months showed mist button actuation force to be normally distributed and (b) (4), with > 0.9990 reliability at 95% confidence; thus, meeting specification. At 12 months, the mean force required to depress the mist button was 0.899 lb. (SD 0.1251). (Found in TR-17321 and TR-17332)

Table 15: Mist Button Actuation Force Test Summary

Requirement	Criteria	Sample Size	Result ¹	Outcome
(b) (4)				PASS

¹ Results shown are for both Time 0 and 12 months.

Engineering Reviewer Comment: The sponsor has not provided justification for the force limits. A request will be made for them to provide justification. **INFORMATION NEEDED**

To evaluate forces associated with assembly and separation of the Mydcombi dispenser cartridge and base components, 20 dispensers were tested. A calibrated force gauge was used to measure the force required to press the cartridge and base together until an audible click indicated assembly. Similarly, the gauge was used to measure force required to separate the cartridge and base.

The dispenser assembly force specification is (b) (4). Test data at Time 0 and 12 months showed dispenser assembly force to be normally distributed and (b) (4) with > 0.9990 reliability at 95% confidence; thus, meeting specification. At 12 months, the mean force required to assemble the cartridge and base was 1.844 lb. (SD 0.4740). (Found in TR-17321 and TR-17332)

Forces required to depress cartridge release tabs (allowing disconnection of the cartridge from the base) and to separate the cartridge from the base were performed only after 12-month accelerated aging. Test data showed the force to depress cartridge release tabs and the force to separate the cartridge from the base to be normally distributed and within specification with

reliability > 0.9900 at 95% confidence. The mean force required to depress cartridge release tabs was 1.524 lb. (SD 0.1455), while the mean force to separate the cartridge from the base was 7.051 lb. (SD 1.802). (Found in TR-17321 and TR-17332)

Table 16: Dispenser Assembly/Retention Force Test Summary

Requirement	Criteria	Sample Size	Result	Outcome
			(b) (4)	PASS
				PASS
				PASS
				PASS

¹ Results shown are for both Time 0 and 12 months.

Engineering Reviewer Comment: The sponsor has not provided justification for the force limits. A request will be made for them to provide justification. **INFORMATION NEEDED**

Spray Testing:

Dispenser spray volume was evaluated in assembled dispensers containing distilled water. Dispenser cartridges had been sterilized and transit-conditioned prior to testing. Each cartridge was paired with a base using firmware as qualified in Section 3.2.P.7.4.4. After assembly, each dispenser was primed to move the water into the fluid path, then sprayed approximately 300 times (Time 0 test) or 350 times (12-month test) into a dish and spray weight was measured.

Test requirements, performance criteria, and outcomes are summarized in Table 17. Test results met all applicable acceptance criteria at Time 0 and at 12 months. Test data at Time 0 and 12 months showed spray volume (b) (4) µL with > 0.9500 reliability at 95% confidence; thus, meeting specification. (Found in TR-17321 and TR-17332)

Table 17: Spray Volume Test Summary

Requirement	Criteria ¹	Sample Size	Result	Outcome
			(b) (4)	PASS

Engineering Reviewer Comment: The sponsor has not provided sufficient information about the dosing size and consistency. They have not included information about dosage consistency after the drug has been allowed to dry on

the apertures after drug delivery. This scenario may lead to fowled or clogged opening that influences the dosage size. Therefore, a deficiency will be communicated to the sponsor asking for the testing or justification as to why it was not provided. **NOT ACCEPTABLE**

Spray diameter and the accuracy associated with spray administration was evaluated using 20 Mydcombi cartridges paired with a base using firmware as qualified in Section 3.2.P.7.4.4. (b) (4)



Table 18: Spray Diameter Test Summary

Requirement	Criteria	Sample Size	Result	Outcome
			(b) (4)	PASS

¹ Results shown are for both Time 0 and 12 months.

² 12-month results only; evaluation not performed at Time 0.

Engineering Reviewer Comment: The sponsor has provided sufficient information about the spray diameter size and consistency. Therefore, the spray diameter size is acceptable. However, it should be noted that the diameter range is quite large (b) (4) This may have an effect on dosage size. However, we defer this to CDER for concerns. **ACCEPTABLE BUT WITH CONCERNS FOR CDER**

The time required for completion of a spray was evaluated using a high-speed camera. Five (5) Mydcombi cartridges containing distilled water, paired with a Mydcombi base using firmware as qualified in Section 3.2.P.7.4 were evaluated. As summarized in Table 19, at Time 0 and 12 months, spray volume within specification was delivered within (b) (4) for each of the 5 dispensers tested; thus meeting the design requirement. (Found in TR-17321 and TR-17332)

Table 19: Spray Delivery Time Test Summary

Requirement	Criteria	Sample Size	Result ¹	Outcome
			(b) (4)	PASS

¹ Results shown are for both Time 0 and 12 months.

Engineering Reviewer Comment: The sponsor has provided sufficient information about the spray delivery time. The time of delivery is less than (b) (4) Therefore, the spray volume testing is acceptable. **ACCEPTABLE**

Shelf Life Testing:

Mydcombi cartridges are labeled with a shelf life of (b) (4) months. Shelf-life testing was performed

as an aspect of the overall cartridge design verification and validation as described in this Section 3.2.P.7.4.

After transit conditioning, sterile packaged Mydcombi cartridges were subjected to accelerated aging (b) (4) then package integrity and functional characteristics and performance testing was performed. All cartridges met applicable acceptance criteria (TR-17332)

Mydcombi bases are labeled with a shelf life of (b) (4) months. As with the Mydcombi cartridge, shelf-life testing was performed as an aspect of overall base design verification and validation as described in this Section 3.2.P.7.4.

Bases were real-time aged for a period of (b) (4) months in a controlled environment with temperature range (b) (4). Transit and conditioning testing were then performed, the bases were charged, scoped before cycling (b) (4) times to verify functionality, then performance was tested. All bases met acceptance criteria, as shown in Table 21. (TR-17224)

Table 21: Base Performance Testing – 28 Month Real-Time Aging

Requirement	Specification	Sample Size	Outcome
(b) (4)			PASS ¹
			Pass
			Pass

Importantly, mean mist button actuation force was (b) (4) which is consistent with the force measured at Time 0. Spray volume testing using cartridges paired with 10 aged bases was conducted before and after bases were stressed by cycling (b) (4) times to simulate active usage. This testing showed no discernable difference in the mean volume dispensed after (b) (4) dosing cycles, as shown below.

Status	Mean Volume (µL)	St. Dev	Min	Max
(b) (4)				

Engineering Reviewer Comment: The sponsor has provided sufficient information about the actuation force and the mean dosage volume over the course of (b) (4) doses. It has shown that there is little variation over the lifetime of the cartridge. Therefore, the testing is acceptable. ACCEPTABLE

Engineering Reviewer Comment Summary: *The sponsor has provided information about the performance over the lifetime of the device and transit testing as well. However, they have not provided information about the force limits for the actuation force, cartridge assembly and separation, or the priming force. Therefore, they will be asked to justify the force testing.*

CONCLUSION:

Engineering Reviewer Comment (After Sponsor Response):

These comments about the force testing limits and shelf life performance testing were sent to CDER on 1/30/23 and sent to the sponsor on 2/8/23. The sponsor responded to the request on 2/24/23. After review of the responses, they were found to be acceptable. Below is the rationale and review of the sponsor responses.

The following engineering comments should be sent to the sponsor in response to the testing that was provided:

1. In your submission, you have provided testing details for the drug dispensing device (Section 3.2.P.7 Container Closure System). However, you have not provided justification for the force requirements in the testing for the mist button actuation force (Section 7.4.2.2), cartridge assembly and separation (Section 7.4.3), or the priming force (Section 7.4.2.1). While you have provided sufficient testing for these device evaluations, you have not provided information about how the limits were chosen for these assessments. It is essential to know the reasoning for the limits as any limit set above a given value may prevent the effective use of the device by the end user. Please provide the justification of the force acceptance limits for the mist button actuation force, cartridge assembly and separation, or the priming force.

Sponsor Response (Letter dated 2/24/23):

(b) (4)



Engineering Reviewer Comment:

*The sponsor has cited ANSI standards for human factors engineering design of medical devices (ANSI HE75). The sponsor has adequately cited the force testing conditions that are discussed in the standard. Although the ANSI standard is only partially recognized by the FDA. However, this partial recognition does not impact the acceptability of the limits. Additionally, the file also had additional human factors reviewers from CDER, who also did not have issues with the limits in their review. Therefore, the justification is adequate from an engineering perspective and the concerns with the testing limits have been resolved. **RESOLVED***

2. In your submission, you include spray volume testing (Section 3.2.P.7 Container Closure System). However, the interval between the sprays was not specified. Please clarify if you conduct testing for consistency of the spray volume in a case that the residual drug is allowed to dry after delivered dosages. This is a concern because the residual drug after delivery may dry in the fluid path or result in the fouling of the ejector holes or nozzle aperture, resulting in the administration of less than intended dosage of the drug. Please provide this testing or justification as to why the testing was not performed in this manner.

Sponsor Response (Letter dated 2/24/23):

Engineering Reviewer Comment:

*The sponsor has provided information that the device was tested over 35 days, a period that is sufficient to demonstrate the lack of fouling at the nozzle. Therefore, this concern has been addressed and the response is adequate. **RESOLVED***

RECOMMENDATION: Completed – No Deficiencies (CND)

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
05/01/2023 02:37:18 PM

NDA 215352

Product Quality Assessment (Addendum #1 to Review #1)

From: Chunchun Zhang, SPQA, Branch 6, ONDP/OPQ

Date: Oct 8, 2021

Re: NDA 215352, MydCombi (Tropicamide /Phenylephrine Hydrochloride
Ophthalmic Spray), 1%/2.5%

NDA 215352 MydCombi (Tropicamide /Phenylephrine Hydrochloride Ophthalmic Spray), 1%/2.5% was recommended for Complete Response from product quality perspective. Refer to IQA dated Sep 24, 2021. The drug product has been switched to a drug device combination product because of the Genus decision. OPPQ recommended to ask the applicant to update 356h form with the device constituent part facilities on Sep 29, 2021. Therefore, NDA 215352 upholds CR recommendation from product quality perspective with the following IR and comments.

The following IR and general comments should be included in the CR letter:

IR:

- *Your proposed product is a drug-device combination product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.*

General comments:

- *In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA)*

and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product.

- Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm>

Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

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
10/08/2021 10:25:57 AM

RECOMMENDATION

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

NDA 215352

Assessment # 1

Drug Product Name	MydCombi (Tropicamide /Phenylephrine Hydrochloride Ophthalmic Spray), 1%/2.5%
Dosage Form	Ophthalmic spray
Strength	1%/2.5%
Route of Administration	Topical ophthalmic spray
Rx/OTC Dispensed	Rx
Applicant	Eyenovia, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Dec 28, 2020	All disciplines
Quality Amendment	Feb 22, 2021	Quality microbiology
Quality Amendment	Mar 15, 2021	Facility and manufacturing process
Quality Amendment	Mar 31, 2021	Drug product
Quality Amendment	Apr 7, 2021	Drug product
Quality Amendment	Apr 28, 2021	Drug product
Quality Amendment	May 12, 2021	Quality microbiology
Quality Amendment	May 20, 2021	Manufacturing process
Quality Amendment	May 25, 2021	Quality microbiology
Quality Amendment	Jun 9, 2021	Quality microbiology
Quality Amendment	Jun 17, 2021	Quality microbiology
Quality Amendment	Aug 9, 2021	Quality microbiology
Quality Amendment	Aug 13, 2021	Quality microbiology
Quality Amendment	Aug 27, 2021	Quality microbiology
Quality Amendment	Sep 13, 2021	Quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Daniel Jansen	Suong Tran
Drug Product	Elise Luong	Chunchun Zhang

Manufacturing process and facilities	Tianhong Zhou	Erin Kim
Microbiology	Catherine Gilbert	Jennifer Sykora (secondary) / Jesse Wells (Tertiary)
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Elise Luong	Chunchun Zhang

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)	(b) (4)	Adequate	6/9/2021	Reviewed by Daniel Jansen
	II			Adequate	12/31/2018	Reviewed by Yun Wang
	III			Not reviewed, information provided in the NDA submission		
	III			Not reviewed, information provided in the NDA submission		
	V			Not reviewed, information provided in the NDA submission		

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

Document	Application Number	Description
IND	135936	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	8/3/2021	Maria Rivera
CDRH (ICCR# 00057876)	Complete	Inadequate	9/3/2021	Keith Christopher
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, and manufacturing process aspects.

*The compliance status of the drug product manufacturing facility, (b) (4) was determined unacceptable based on the most recent inspection performed ending (b) (4), the response to the 483 observations were not complete at the conclusion of this assessment. Therefore, OPMA issued an overall recommendation of "Withhold" on Sep 22, 2021. Additionally, there are outstanding deficiencies from the quality microbiology perspective. CDRH was consulted to review the Optejet dispenser and has found three major deficiencies in the consult memo dated on 9/3/2021. In agreement with the above recommendation, NDA 215352 is recommended **Complete Response** from Product Quality perspective.*

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

The product was determined to be a drug device combination product per the Genus decision in Sep 2021. Dr. James Bertram (CDRH) confirmed that only a technical/engineering consult review is necessary from CDRH for this product and the device manufacturing facility is acceptable based on the inspection history on (b) (4). Dr. Keith Christopher (CDRH) conducted an engineering review on Optejet dispenser on Sep 3, 2021. Additionally, the following comment related to the combination product should be included in the action letter:

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs.

In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the “device” definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product.

The following CR comments should be included in the Action Letter:

Facilities deficiency:

During a recent inspection of the (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Microbiology deficiencies:

1. The (b) (4) microbial ingress container closure integrity testing (CCIT) performed (b) (4) is acknowledged, (b) (4)

Please consider the following options to demonstrate the integrity of the assembled device:

a. (b) (4)

b. (b) (4)

(b) (4)

c.

2. *It is acknowledged that the Alcami facility has performed* (b) (4)

Provide the results of this hold time study.

3. *The validation information for* (b) (4)
acknowledged. Please address the following:

(b) (4)

(b) (4)

CDRH deficiencies:

1. *In your submission (p. 11), you have stated that the*

(b) (4)

*Please clarify the electrical
component of your device.*

2. In your submission (p. 13), you have stated that the device is

(b) (4)

Please clarify the reusability of the device in order to determine if additional testing is needed.

3. In your submission (p.21), you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:

a. You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.

b. Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.

c. Leak testing should be performed

(b) (4)

d. Performance testing to confirm that the device does deliver of fluid with each actuation and that there is a low variance of volume delivered. High variance leads to improper dosage which will impact performance of the drug formulation and is a safety and effectiveness concern.

(b) (4)

e. Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.

f. You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of

the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-time and accelerated aging, sterilization, and transit testing.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Tropicamide /Phenylephrine Hydrochloride ophthalmic spray is a sterile, clear, colorless solution fixed-dose combination of tropicamide 1% (80 µg/8 µL) and phenylephrine Hydrochloride 2.5% (200 µg/8 µL) ophthalmic spray packaged in (b) (4) 2 mL glass vial and then enclosed into a sterile Optejet dispenser. Each metered spray delivers 8µL which contains 80 µg tropicamide and 200 µg phenylephrine Hydrochloride. Currently only Tropicamide ophthalmic solution and Phenylephrine Hydrochloride ophthalmic solution are approved products and both have USP monographs.

Proposed Indication(s) including Intended Patient Population	For the treatment of inducing mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired
Duration of Treatment	One metered spray should be administered as required, up to a maximum of 3 sprays per eye per day
Maximum Daily Dose	Tropicamide 480µg and Phenylephrine Hydrochloride 1200µg. See the package insert for details
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Drug substances Tropicamide, USP and Phenylephrine Hydrochloride, USP are synthetic small molecules and white to practically white odorless crystals. The applicant cross-referenced the CMC information for the drug substances to DMF (b) (4) and DMF (b) (4) respectively. Both DMFs are currently adequate.

Drug Product: Adequate

Tropicamide /Phenylephrine Hydrochloride ophthalmic spray is a sterile, clear, colorless solution. All the excipients are compendial.

The revised drug product specifications are acceptable and include the following quality attributes: appearance, ID, pH, osmolality, assay, impurities, viscosity, minimum fill, particulate matter, sterility and benzalkonium chloride assay. Any unspecified impurity/degradant controlled at NMT (b) (4) % for Tropicamide was found acceptable by pharm/tox reviewer Dr. Maria Rivera on 8/3/2021. All the analytical methods are validated. 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 clinical batch and three registration batches manufactured at (b) (4) site with the commercial scale of (b) (4) and one registration batch manufactured at Alcami at (b) (4) are provided. The product is packaged in a (b) (4) 2 mL glass vial with an Optejet dispenser which was reviewed by CDRH Dr. Keith Christopher with 3 major deficiencies to be included in the action letter.

The applicant has submitted 12 months stability data at long term (25°C/60%RH) and 6 months at accelerated condition (40°C/75%RH) for three registration batches manufactured at (b) (4) site and 3 months data at long term and accelerated condition for one registration batch at Alcami. All the other quality attributes met the specifications. (b) (4)

Therefore, the expiration date of 24 months is granted when stored at (b) (4) °C- 25 °C.

The storage statement is "Store at (b) (4) °C-25°C (b) (4) °F-77°F)" " (b) (4) " 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: Inadequate

The manufacturing process includes: (b) (4)
(b) (4) The applicant adequately responded to all identified process deficiencies. (b) (4) (b) (4) FEI (b) (4) the alternate Drug Product manufacturing facility, is not acceptable from the recent inspection. The corrective actions to address 483 observations have not been provided at the time of this review. All the other facilities are acceptable based on the inspection or profile.

Biopharmaceutics: N/A

Microbiology (if applicable): Inadequate

The drug product is (b) (4)
There are outstanding issues related to inadequate CCIT
on the fully assembled cartridge; (b) (4)
Microbiology
deficiencies will be included in the action letter.

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	
Impurities	- Formulation - Container closure - Process parameters - Scale/equipment	H		M	
pH	- Formulation - Container closure - Process parameters - Scale/equipment	L		L	
Particulate matter	- Formulation - Container closure - Process parameters - Scale/equipment	L		L	
Optejet dispenser	- Formulation - Container closure	H		H	
Sterility	- Formulation - Container closure - Process parameters - Scale/equipment	H		M	

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

Labeling comments will be communicated to OND during the labeling discussion.

5. Manufacturing Deficiencies

During a recent inspection of the (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

1. The (b) (4) microbial ingress container closure integrity testing (CCIT) performed (b) (4) is acknowledged, (b) (4)

Please consider the following options to demonstrate the integrity of the assembled device:

a.

b.

(b) (4)

c.

2. It is acknowledged that the Alcamí facility has performed

(b) (4)

Provide the
results of this hold time study.

3. The validation information

(b) (4)

is acknowledged.
Please address the following:

(b) (4)

(b) (4)

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

CDRH deficiencies on Optejet dispenser

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Sep 24, 2021

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental Analysis (EA)

In accordance with 21 CFR 25.31(b), Eyenovia, Inc. hereby claims a categorical exclusion from the requirement to prepare an Environmental Assessment, as chemical waste materials generated in the laboratories serviced by the contracts administered by FDA will be disposed of in compliance with all applicable Federal, State, and local requirements.

In accordance with 21 CFR 25.31 (a), Eyenovia also claims a categorical exclusion from the requirement to prepare an Environmental Assessment as it does not increase the use of the active moiety, since the two active moieties of commercially approved drug product, i.e. phenylephrine hydrochloride ophthalmic solution and tropicamide ophthalmic solution are combined to manufacture Eyenovia's tropicamide 1%/phenylephrine hydrochloride 2.5% ophthalmic spray. Therefore, the Eyenovia fixed combination product is anticipated to displace the use of one or both of the currently marketed products and thus would not increase the use of the two active moieties in the environment.

Assessment: Adequate from a CMC perspective.

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 06/28/2021.

Secondary Assessor Name and Date (and Secondary Summary, as needed): ChunChun Zhang, Ph.D.; 08/23/2021 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	MydCombi	On 03/08/21, DMEPA found the proposed proprietary name is acceptable.
Established name(s)	Tropicamide	Adequate
	Phenylephrine HCl	Adequate
Route(s) of administration	Topical ocular	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tropicamide 1% and Phenylephrine HCl 2.5% Ophthalmic Spray Each metered spray delivers 8 µL which contains 80 µg tropicamide and 200 µg phenylephrine HCl	Adequate

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	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.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

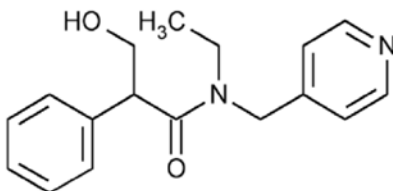
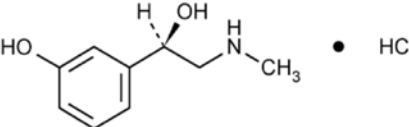
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Depression of the Load Button followed by a depression of the Dose activation button sequentially cycled 5 times (known as Dispenser Priming) (b) (4) . On the 6th cycle, the dose activation button, located on the rear of the dispenser, is depressed by the user, thus delivering the dose. In addition, a priming step must be performed before use of MydCombi each day.	Adequate. There is a separate document (11 pages) of Instruction For Use MydCombi™

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)	Metered-spray solution	Adequate
Strength(s) in metric system	Tropicamide 1% (w/w) 80 mcg per spray Phenylephrine HCl 2.5% (w/w) 200 mcg per spray	CMC comments were conveyed to OND.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	MydCombi is a clear, colorless, sterile topical ophthalmic spray containing Tropicamide 1% and Phenylephrine 2.5%	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name	MydCombi	On 03/08/21, DMEPA found the proposed proprietary name is acceptable.
Established name(s)	Tropicamide Phenylephrine HCl	
Dosage form(s) and route(s) of administration	Metered-spray solution and ocular topical	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Equivalent to 200 mcg of phenylephrine base	CMC comments were conveyed to OND.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Benzalkonium chloride Hydrochloric acid Sodium hydroxide Water for Injection	Adequate
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.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This product is sterile prior to connecting to the Optejet Dispenser, a drug delivery system	Adequate

Pharmacological/ therapeutic class	Tropicamide is a (b) (4) anticholinergic Phenylephrine is a (b) (4) agonist	CMC comments were conveyed to OND.
Chemical name, structural formula, molecular weight	<u>Tropicamide</u> Benzeneacetamide, N-ethyl- α-(hydroxymethyl)-N-(4- pyridinylmethyl)-  Molecular weight: 284.35 g/mol $C_{17}H_{20}N_2O_2$ <u>Phenylephrine Hydrochloride</u> (R)-3-hydroxy- α[(methylamino)methyl]benz enemethanol hydrochloride  Molecular weight: 203.67 g/mol $C_9H_{13}NO_2 \bullet HCl$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Section 3.2.S.1.3	Adequate

If radioactive, statement of important nuclear characteristics.	N/A	N/A
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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	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	There is no misleading statement on the labels	Adequate

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)	Metered-spray solution	CMC comments were conveyed to OND.
Strength(s) in metric system	Tropicamide 1% (w/w) 80 mcg per spray Phenylephrine HCl 2.5% (w/w) 200 mcg per spray	CMC comments were conveyed to OND.
Available units (e.g., bottles of 100 tablets)	Mydcombi is supplied as sterile solution in a 2 mL vial enclosed in a dispenser cartridge.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, colorless, (b) (4) sterile aqueous solution having a pH between 4.0 and (b) (4)	CMC comments were conveyed to OND.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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.	N/A	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not tamper with or attempt to open the Mydcombi cartridge. Such action may damage the dispenser causing an incorrect medication discharge volume; additionally, the dispenser base may not function properly. Store at 25°C/65% RH. 	Adequate There is a discrepancy in the storage temperature in the labeling. For example, the Package Insert lists storing at (b) (4) °C to 25 °C, whereas the Instruction for Use and the container labels list 15 °C to (b) (4) °C. This is confusing. CMC has communicated this issue with the labeling team and request that the storage temperature be revised to 'store at (b) (4) ° - 25°C (b) (4) ° - 77°F).
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	N/A
Storage conditions. Where applicable, use USP storage range rather than	Store between at (b) (4) 25°C (68° -77°F).	There is a discrepancy in the storage temperature in the labeling. For example, the

storage at a single temperature.	(b) (4)	Package Insert lists storing at (b) (4) °C to 25 °C, whereas the Instruction for Use and the container labels list 15 °C to (b) (4) °C. This is confusing. CMC has communicated this issue with the labeling team and request that the storage temperature be revised to 'store at (b) (4) ° - 25°C (68° - 77°F)'.
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	N/A
Include information about child-resistant packaging	N/A	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.

In this NDA, the labeling contains an additional document titled **INSTRUCTIONS FOR USE MYDCOMBI™**. Contents highlighted below:

(b) (4)

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	Alcami Corporation (b) (4)	CMC comments were conveyed to OND.

2.0 PATIENT LABELING

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

Labeling will be finalized through OND during labeling negotiations with the applicant.

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

180 Metered Sprays in a 2 mL Glass Vial in an Optejet Dispenser Spraying Drug Delivery System

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	MydCombi Tropicamide Phenylephrine HCl	On 03/08/21, DMEPA found the proposed proprietary name is acceptable.
Dosage strength	Tropicamide 1% (w/w) 80 mcg per spray Phenylephrine HCl 2.5% (w/w) 200 mcg per spray	CMC comments were conveyed to OND.
Route of administration	Ophthalmic spray	Adequate
Net contents (e.g. tablet count)	(b) (4) mL filled volume in a 2 mL glass vial, total 180 sprays per vial	CMC comments were conveyed to OND.
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F)/65% RH	CMC comments were conveyed to OND.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The product does not contain alcohol.	Adequate
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Eyenovia, Inc. 295 Madison Avenue, Suite 2400, New York, NY 10017	Adequate
Medication Guide (if applicable)	There is a separate document (11 pages) of Instruction For Use MydCombi™	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
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.	Drug product is a novel fixed ratio combination of Tropicamide and Phenylephrine HCl. There is no USP standard.	Adequate
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling:

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant. CMC team has the following comments for the labeling review team:

1. *Drug product labeling review of Full Prescribing Information, we have the following comments:*
 - (a) *In section 3 Dosage Forms and Strengths, add 'each metered spray delivers 8 microliters of mist containing 80 mcg tropicamide and 200 mcg phenylephrine HCl.*
 - (b) *In section 11 Description, when the active ingredient is a salt, apply the USP Salt Policy per FDA guidance. Hence, list the equivalent amount (in mcg) of phenylephrine base per 8 microliters spray. Modify all container labels to include this information.*
 - (c) *In section 11 Description, also provide the equivalent amount of phenylephrine base per mL.*
 - (d) *In section 11 Description, also provide the Pharmacological/therapeutic class.*
 - (e) *In section 16 How Supplied/Storage and Handling, clearly state the dispenser cartridge is metered spray, because this is how you described in the NDA.*
 - (f) *In section 16 How Supplied/Storage and Handling, also add a row to list the strength(s) (in metric system).*
 - (g) *In section 16 How Supplied/Storage and Handling, clearly state the product is a clear, colorless, (b) (4) sterile (b) (4) solution having a pH between 4.0 and (b) (4).*
 - (h) *In section 16 How Supplied/Storage and Handling, change 'store at room temperature (b) (4)'. Change the storage temperature on the labels of all containers, including the carton, the bulk-replacement-cartridge, the label-cartridge, the label-product-box, and the label-replacement-cartridge.*
 - (i) *Section 1.2.6 Manufacturing Information is missing, add back this section with the name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer.*
2. *Drug product labeling review of container labels, we have the following comments:*
 - (a) *The labels should show 'each metered spray contains 80 mcg Tropicamide 1% (w/w) and 200 mcg Phenylephrine HCl 2.5% (w/w). Add this statement on all container labels.*

(b) The labels should show the total number of spray expected from a (b) (4) mL filled volume.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

Other than the comments listed on page 102 and 103, the product labels are acceptable from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Primary Labeling Assessor Name and Date: *Elise Luong, Ph.D., 06/24/21.*

Secondary Assessor Name and Date (and Secondary Summary, as needed): *ChunChun Zhang, Ph.D., 08/23/21.*



Elise
Luong

Digitally signed by Elise Luong
Date: 8/23/2021 08:40:45AM
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Chunchun
Zhang

Digitally signed by Chunchun Zhang
Date: 8/23/2021 09:19:58AM
GUID: 51269608000064178e75377202fe6c5d

CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	215352
Assessment Cycle Number	1
Drug Product Name/ Strength	Tropicamide 1%/Phenylephrine HCl 2.5% Ophthalmic Spray (MydCombi)
Route of Administration	Topical Ophthalmic Spray
Applicant Name	Eyenovia, Inc.
Therapeutic Classification/ OND Division	CDER/OSM/Division of Ophthalmology
Manufacturing Site	Alcami Corporation: (b) (4) FEI: (b) (4)
Method of Sterilization	

Assessment Recommendation: Inadequate

Assessment Summary:

The drug product is (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original (0001)	12/28/2020
Microbiology IR Response (0003)	02/22/2021
P/F IR Response (0004)	03/15/2021
DP IR Response (0005)	03/31/2021
DP IR Response (0006)	04/07/2021

DP IR Response (0008)	04/28/2021
Microbiology IR Response (0010)	05/12/2021
Microbiology IR Response (0013)	05/25/2021
Microbiology IR Response (0014)	06/09/2021
Microbiology IR Response (0015)	06/17/2021
Microbiology IR Response (0016)	08/09/2021
Microbiology IR Response (0017)	08/13/2021
Labeling IR Response (0018)	08/23/2021
Microbiology IR Response (0019)	08/27/2021
Microbiology IR Response (0021)	09/13/2021

Highlight Key Issues from Last Cycle and Their Resolution: Issues regarding (b) (4) were identified in the Microbiology Filing Review for this NDA.

Remarks: This is an eCTD submission. A comparability protocol was provided regarding (b) (4).

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

- Inadequate CCIT on the fully assembled cartridge
- Inadequate (b) (4)
- Inadequate hold time studies (b) (4)
- Inadequate (b) (4)

Supporting Documents:

(b) (4)

(b) (4)

Select Number of Approved Comparability Protocols: 1

Note to Reviewer: The applicant notes that this DP is intended to be dispensed with their Optejet Dispenser, which may be referred to throughout the application as MiDD. The DP may also be referred to as (b) (4). DMA was notified that the dispenser is considered to be part of the DP under 21 CFR 200.50, and is not a combination product or a device. Therefore, DMA will perform the review of the microbiological control of the dispenser.

The following IRs were sent to the applicant on 02/08/2021:

(b) (4)

In their SN 0003 (02/22/2021) IR response, the applicant stated that all commercial batches of the drug product vial will be manufactured at the Alcami, Inc. facility in (b) (4). Validation information for this facility is provided in DMF (b) (4). A Letter of Authorization for DMF (b) (4) containing specific locations of validation information was provided in SN 0003 document "Letter of Authorization – DMF (b) (4) –

Alcami,” dated 2/18/2021. The applicant stated in their SN0003 IR response that commercial manufacturing will not occur at the (b) (4) (b) (4) facility, however as of the 4/28/2021 submission, (b) (4) is still listed as a secondary DP manufacturer. Additionally, the Alcamí (b) (4) facility is listed as a Primary Manufacturer. Clarification was requested.

The following IR was sent to the applicant on 05/10/2021:



In their SN0010 IR response, the applicant stated that they do intend to perform (b) (4). Therefore, (b) (4) will be evaluated as a drug product manufacturer in this review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product** – MydCombi (tropicamide 1% and phenylephrine HCl 2.5%), is a sterile, clear, colorless topical ophthalmic spray indicated to induce mydriasis for routine diagnostic procedures and when short term pupil dilation is desired.
- **Drug product composition** –

Ingredient	Concentration (% w/w)	Function
Phenylephrine HCl, USP	2.5	API
Tropicamide, USP	1.0	API
(b) (4) ® Benzalkonium Chloride (b) (4) USP/NF	0.01	Preservative
Hydrochloric acid, USP	q.s.	pH Adjustment
Sodium hydroxide, USP	q.s.	pH Adjustment
WFI, USP	q.s.	(b) (4)

- **Description of container closure system** –

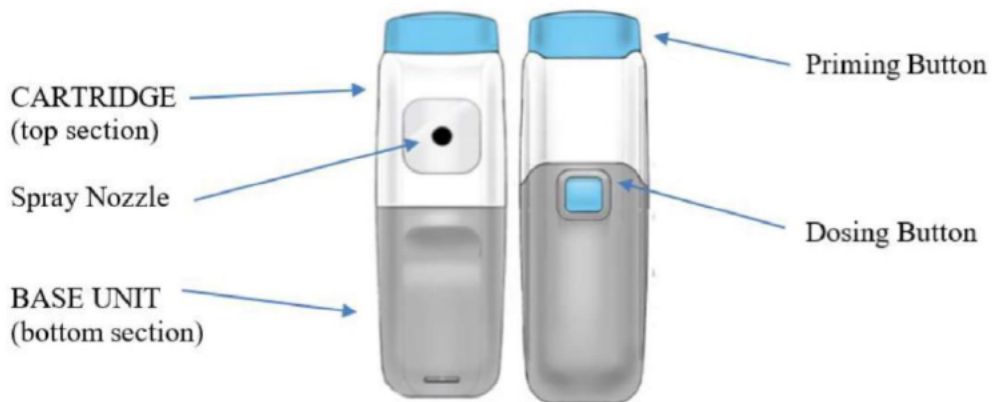
Component	Packaging	Description	Manufacturer
Vial	Primary		(b) (4)
Stopper	Primary		
Seal	Secondary		
Cartridge	Primary		
Cartridge tray	Secondary		
Base	Secondary		

The drug product solution is

(b) (4)

During use, the vial remains intact until the device is primed, after which the vial stopper is punctured and the drug product solution travels through the fluid path in the cartridge. Therefore, the device cartridge is considered part of the primary container (SN0001: Section 3.2.R “protocol-comparability,” diagrams taken from pages 5-6).

**Figure 1: Eyenovia Microdose Delivery (Optejet)
Front (Left) and Back (Right) Views**



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Assessment: The applicant has adequately described the drug product composition and the container closure system designed to maintain product sterility.

Adequate

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Memorandum

DATE: August 30, 2021

FROM:

Keith Christopher, PhD
Chemical Engineer
Glaucoma, Cornea, and Surgical Devices Team
CDRH/OPEQ/OHT1/DHT1A

TO:

Record through
Lead Reviewer: Damia Jackson

SUBJECT: ICC2100163, Engineering Review
Eyenovia Inc.

DEVICE: MiDD (Microdose Dispenser)

RECOMMENDATION: Additional feedback needed

BACKGROUND:

Eyenovia is pursuing development of [REDACTED] (b) (4)
[REDACTED] a fixed combination formulation containing phenylephrine (PE) hydrochloride and
tropicamide (Trop) to dilate the pupil (mydriasis).

INDICATIONS FOR USE:

Mydriasis in routine diagnostic procedures and in conditions where short term pupil
dilation is desired.

DEVICE DESCRIPTION:

The Eyenovia MiDD is designed to accurately deliver precise low-volume doses of topical
ocular pharmaceutical ingredients. [REDACTED] (b) (4)

As shown in Figure 1, the MiDD is composed of a “cartridge assembly” (shown in white in the
the image below) and the base unit (shown in gray in the image below).

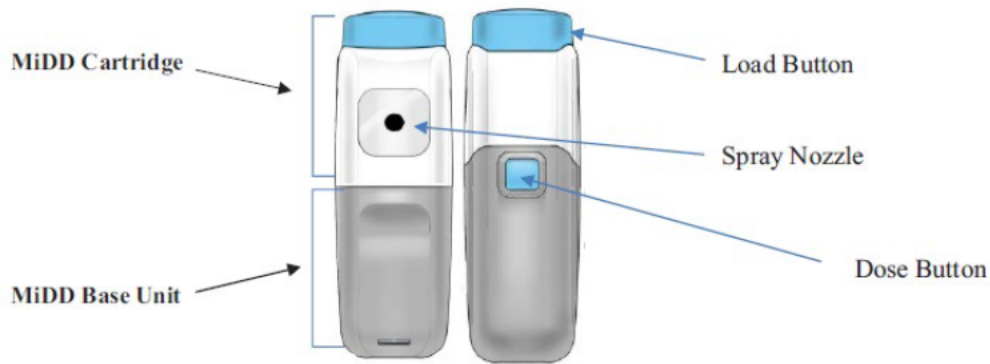


FIGURE 1: EYENOVIA MiDD FRONT (L) AND BACK (R) VIEW

Figure 2 is a diagram of the MiDD base unit and cartridge assemblies.

The cartridge assembly is the primary container closure system, which contains (b) (4)

The user of the MiDD administers the drug product by taking the following steps: Prior to initial MiDD use, the Load Button (top of cartridge assembly) is depressed to puncture the vial seal, creating a fluid path for drug administration. At the time of drug administration, the Load Button is again depressed to activate the precise fluid dosing mechanism that fills the nozzle assembly creating the aerosol of the drug, then the Dose Button at the back of the MiDD base unit is pressed to activate the (b) (4) element creating the aerosol constituting the drug dose exiting the system through the Spray Nozzle.

MiDD dose volume is controlled by the physical/chemical properties of the drug formulation and the MiDD electrical mechanical system is tuned to the specific properties of each drug formulation.

Engineering Reviewer Comment: The sponsor states that the dose volume is controlled by physical/chemical properties of the drug formulation, which I am assuming is dependent on the (b) (4)

However, it is not clear (b) (4)

Sponsor may be requested to clarify the electrical component. (b) (4)

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CONCLUSION:

The sponsor has omitted several key tests that are required to demonstrate the safety and effectiveness of the device and there are some points that require clarification from the sponsor. The following should be communicated to the sponsor:

1. In your submission (p. 11), you have stated that the (b) (4)

(b) (4) Please clarify the electrical component of your device.

2. In your submission (p. 13), you have stated that the device i (b) (4)
Please clarify the reusability of the device in order to determine if additional testing is needed.

3. In your submission (p.21), you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:
- You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping the has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.
 - Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.
 - Leak testing should be performed (b) (4)
 - Performance testing to confirm that the device does deliver (b) (4) of fluid with each actuation and that there is a low variance of volume delivered. High variance leads to improper dosage which will impact performance of the drug formulation and is a safety and effectiveness concern.
 - Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.
 - You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-time and accelerated aging, sterilization, and transit testing.

RECOMMENDATION: Additional feedback needed

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/s/

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