CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215352Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 28, 2023

To: Michael Puglisi, Senior Regulatory Health Project Manager
Office of Regulatory Operations, Division of Regulatory Operations for Specialty Medicine

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5%, for topical ophthalmic use

NDA: 215352

Background:
In response to the Division of Regulatory Operations for Specialty Medicine (DROSM) consult request dated March 14, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5%, for topical ophthalmic use (MYDCOMBI).

PI/IFU:
OPDP's review of the proposed PI and IFU is based on the draft labeling emailed to OPDP on March 14, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on March 14, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or Carrie.Newcomer@fda.hhs.gov.

29 Page(s) of Draft Labeling 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/

CARRIE A NEWCOMER
03/28/2023 10:10:02 AM

LABEL LABELING AND HUMAN FACTORS VALIDATION RESULTS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

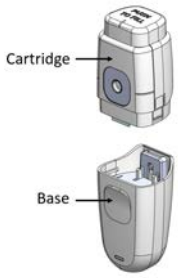
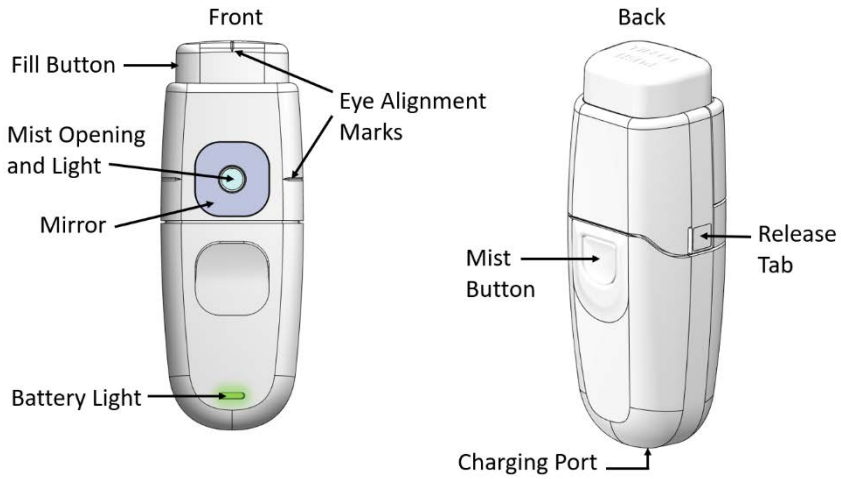
Date of This Review:	February 23, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 215352
Product Name, Dosage Form and Strengths:	MydCombi (tropicamide and phenylephrine HCl) ophthalmic spray, 1%/2.5%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eyenovia, Inc.
FDA Received Date:	November 08, 2022, and December 19, 2022
TTT ID #:	2022-2759 and 2022-2760
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS.
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Human Factors Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint MBA, PMP

1 REASON FOR REVIEW

This review evaluates a human factors (HF) validation study report, labels and labeling submitted under a New Drug Application (NDA) 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5%), Ophthalmic Spray. The Division of Ophthalmology (DO) requested that we review the proposed HF validation study report, labels, and labeling for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT DESCRIPTION

Table 1: Relevant Products Information	
Initial Approval Date	N/A
Active Ingredient (Drug or Biologic)	Tropicamide and phenylephrine HCl
Indication	To induce mydriasis for routine diagnostic procedures and in condition where short term pupil dilation is desired.
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic spray
Strength	Tropicamide: 1% and phenylephrine HCl: 2.5%
Dose and Frequency	In patients 1 year of age or greater: Administer one metered spray to the cornea. (b) (4) [redacted] In pediatric patients less than 1 year of age: One spray should be administered as required, up to a maximum of 3 sprays per eye per day.
How Supplied	Mydcombi is supplied as sterile solution in a 2 mL vial enclosed in a dispenser cartridge. NDC 81046-0111-01. Carton containing one replacement sterile drug cartridge. NDC 81046-0111-02. Box containing one carton with one sterile drug cartridge, and one carton with one base unit.

	NDC 81046-0111-05. Box containing five cartons, each with one replacement sterile drug cartridge. *The Dispenser is comprised of 2 parts – the MydCombi cartridge that holds the drug solution and the Optejet base that holds electronics.
Storage	Store at room temperature ((b) (4) e
Container Closure/Device Constituent	MydCombi Dispenser Parts  MydCombi Assemble 
Intended Users	Optometrists, ophthalmic technicians, and ophthalmologists
Intended Use Environment	Healthcare Setting

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

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; thus, no human factors validation data to demonstrate that the product user interface supports safe and effective use was submitted to the Agency for review.

On August 23, 2021, the Applicant submitted a study report titled, *Evaluation of the Mydcombi Optejet Dispenser Instructions for Use Test Report*. According to the Applicant, this report was submitted in response to a June 29, 2021, request from DO for information regarding the validation of the proposed Mydcombi Instructions for Use in a clinical setting.[a] We note that prior to the study report submission, the Applicant states that they submitted a study protocol on July 22, 2021, for which DO provided comment via email on July 29, 2021. DMEPA was not aware that a study protocol was submitted; thus, we did not review this study protocol.

During the review cycle, NDA 215352 was deemed a drug-device combination product.

In addition to reviewing the prescribing information (PI) and labels and labeling, we conducted a high-level review of the *Evaluation of the Mydcombi Optejet Dispenser Instructions for Use Test Report* and found that the study methodology was not adequate to demonstrate that the user interface supports safe and effective use of the proposed product. The following include some of our methodology concerns:

- There was no use-related risk analysis (URRA) submitted
- There were no critical tasks identified
- The study was designed to validate the instructions for use (IFU), which is only one element of the product user interface.
- Human factors validation testing should assess all points of interaction between the user and the device, including all elements of the device with which the user interacts. The moderator directed each participant to complete each step according to the IFU. This is not reflective of an actual use scenario and would be more appropriate for formative human factors work. In a human factors validation study, we would expect that the scenario presented to the user is reflective of what their experience would be in actual use. For example, in actual use, we don't expect that a moderator will be standing by to instruct the user.

These methodology concerns precluded our ability to conduct a thorough review of the study report. We recommended the Applicant conduct a comprehensive use-related risk analysis and

[a] Re: NDA 215352 MydCombi - Tropicamide 1% and Phenylephrine HCl 2.5%" Ophthalmic Spray - Amendment to NDA Application: Instruction for Use (IFU) Study Report. New York (NY): Eyenovia, Inc. 2021 AUG 23. Available from:\\CDSESUB1\evsprod\nda215352\0018\m1\us\12-cover-letters\cover.pdf

noted that the risk analysis can be used to inform the design of a human factors validation study protocol for their product. We recommended they submit the study protocol for feedback from the Agency before commencing the study.[b]

On October 22, 2021, the Agency sent the Applicant a Complete Response (CR) letter that included the abovementioned human factors recommendations.[c]

On November 08, 2022, the Applicant resubmitted their New Drug Application (NDA) 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5%), Ophthalmic Spray. This submission included human factors (HF) validation study results. The HF study was conducted to evaluate the clarity of the instructions in the Mydcombi Base Charging and Electrical Information Guide only. We note the Applicant did not submit the study protocol for Agency review and feedback before commencing the study. This HF validation study results and the Label and Labeling are the subject of this review.

1.3 MATERIALS REVIEWED

Table 2. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (For Methods and Results)
Previous DMEPA Reviews	A
Human Factors Validation Study Report	B
Information Requests Issued During the Review	C
CDRH Human Factors Consult Review	D
Labels and Labeling	E

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[b] Roosta, N. Label and Labeling Review for MydCombi (tropicamide and phenylephrine HCl) (NDA 215352). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 12. OSE RCM No.: 2020-2736.
[c] Puglisi, M. Complete Response for MydCombi. Silver Spring (MD): FDA, CDER, OND, DO (US); 2021 OCT 22. NDA 215352.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

2.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

<table>
<tr><th colspan="2">Table 3. Study Methodology for Human Factors (HF) Validation Study</th></tr>
<tr><td>Study Design Elements</td><td>Details</td></tr>
<tr><td>User Group(s)</td><td>
<table>
<tr><th>Intended User Type</th><th>n (%)</th></tr>
<tr><td>Optometrists</td><td>7 (46.7%)</td></tr>
<tr><td>Ophthalmic Technicians</td><td>6 (40.0%)</td></tr>
<tr><td>Ophthalmologists</td><td>2 (13.3%)</td></tr>
</table>
</td></tr>
<tr><td>Training</td><td>None of the participants received training prior to participating in the study session. The Prescribing information was provided to the participants and the participants were allowed time to review the products before the evaluation.</td></tr>
<tr><td>Test Environment & Materials</td><td>Conference room or exam room setting.</td></tr>
<tr><td>Sequence of Study</td><td>• Completed pre-test questionnaire
• Test participants were instructed to first read the Mydcombi Base Charging and Electrical Information Guide
• Completed a series of 11 tasks related to the Mydcombi base while referencing the guide.</td></tr>
</table>

3 DISCUSSION

Our review of the study protocol and results identified flaws in the study methodology, such as only evaluating the clarity of the instructions in the Mydcombi Base Charging and Electrical Information Guide, which is only one element of the product user interface. Additionally, there were deficiencies in how the data was collected and documented. For example, the moderator did not probe or investigate why users experienced certain close calls. These flaws limit our ability to interpret the study data and draw a conclusion regarding the ability of the user interface to support the safe and effective use of the product.

3.1 SUMMARY OF HUMAN FACTORS VALIDATION STUDY RESULTS

We have carefully reviewed each observed event, the Applicant's URRA, the participants' subjective feedback, and the Applicant's root cause analysis (RCA). For our analyses see Section 3.2 below.

3.2 ANALYSIS OF TASK ERRORS

The HF validation study showed close calls with the tasks listed below in this section. Based on our review, of the available assessment of these close calls, the available participants' subjective feedback and the Applicant's root cause analysis (RCA) we did not identify areas of improvement to address these close calls, however we provide recommendations in section 4.1 below to address identified flaws in the study methodology discussed in section 3 above. Below is our review of these close calls:

- Operational Temperature Range: there was one close call observed for this task. Per the Applicant's URRA if this task is omitted or not performed correctly, there is risk of Insufficient mydriasis achieved due to insufficient API concentration and burn injury. The RCA indicated that the participant initially overlooked the information but recovered and responded with the correct information. The RCA is incomplete because the Applicant did not investigate why the participant overlooked the information.

- Type of charger and USB cable that can be used with the system: there were two close calls. Participants compared information on page 3 and page 4 before answering correctly. Per the Applicant's URRA if this task is omitted or not performed correctly, there is a risk of user inconvenience. We note the risks are not complete because the Applicant did not specify the clinical impact of this close call. The RCA indicated that the participants struggled to locate the information about the type of charger to use for charging the base. The RCA is incomplete because the Applicant did not investigate why the participants struggled to locate the information about the type of charger to use for charging the base.

- Information regarding electromagnetic compatibility (EMC): there was one close call observed for this task. Per the Applicant's URRA if this task is omitted or not performed correctly, there is a risk of user inconvenience. We note risks are not complete because the Applicant did not specify the clinical impact of this close call to the patient. The RCA indicated that the participants initially indicated the Bluetooth Information but recovered and correctly provided the location for the EMC. The RCA is incomplete because the Applicant did not investigate why the participant initially indicated the Bluetooth Information.

4 HUMAN FACTORS STUDY CONCLUSION AND RECOMMENDATION

Our review of the study methodology identified several flaws which limits our ability to interpret the study data and conclude whether the proposed user interface supports safe and effective use of the product. For example, we note the study only evaluated the clarity of the instructions in the Mydcombi Base Charging and Electrical Information Guide, which is only one element of the product user interface. Additionally, there were deficiencies in how the data was collected and documented. For example, the moderator did not probe or investigate why users experienced certain close calls. We provide recommendations to the Applicant in Section 4.1 to address these flaws. We have determined that the Applicant should conduct another human factors (HF) validation study to validate the entire user interface. We ask that the Division of Ophthalmology (DO) convey these recommendations in its entirety to the Applicant. We recommend that the Applicant revise the study methodology, implement our recommendations, and submit the HF validation study protocol for our review prior to conducting another HF validation study to demonstrate that the proposed user interface supports safe and effective use of the product.

4.1 IDENTIFIED ISSUES AND RECOMMENDATIONS FOR EYENOVIA, INC.

Our evaluation of your human factors (HF) validation study indicates that there were methodology issues that limited our ability to interpret the study data and conclude whether the proposed user interface supports safe and effective use of the product. Please see the Identified Issues and Recommendations list below. We recommend you implement our recommendations below and submit your revised HF study protocol for Agency's review and feedback prior to conducting another HF study to demonstrate that the proposed user interface supports safe and effective use of the product.

Identified Issues and Recommendations

- The study was designed to validate the Mydcombi Base Charging and Electrical Information Guide, which is only one element of the product user interface. Human factors validation testing should assess all points of interaction between the user and the device, including all elements of the device with which the user interacts (e.g., instructions for use, training materials, and any other user labeling, if applicable)[d]. Revise your study methodology to assess all points of interaction between the user and the device, including all elements of the device with which the user interacts.
- The study environment was not representative of the intended use environment for the proposed product. The report indicated the testing was conducted in a "conference

[d] Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. Food and Drug Administration. 2016. Available from https://www.fda.gov/media/96018/download

room or exam room setting." We need to ensure the test environment is representative of the intended use environment to ensure a high-fidelity study. Revise your study protocol to ensure the test environment will simulate the intended use environment. This should include sound, lighting, distractions and supporting equipment and materials.

- There were deficiencies in how the data was collected and documented. For example, the moderator did not probe or investigate why users experienced certain close calls. We are unable to provide a comprehensive review of the study results without the abovementioned information. During the study ensure that the moderator probes or investigate why users experienced certain use errors, close calls and use difficulties to help inform the analysis of the study results.

You can consider submitting your HF validation study protocol for feedback from the Agency before commencing your study. Note that submission of a protocol for review is not a requirement.

The requested information should be submitted to the NDA. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents[e]:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

The following three draft guidance documents represent additional public sources of potential information that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[f]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

[e] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[f] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

4.2 DISCUSSION OF LABELS AND LABELING

On October 12, 2021, we completed review of proposed MydCombi Prescribing Information (PI), Instructions for Use (IFU), cartridge container label, MydCombi Product Box carton labeling, replacement cartridge carton labeling, and the Bulk replacement cartridge box carton labeling received on December 28, 2020 under OSE RCM# 2020-2736.[g] We compared the new PI and IFU received on November 8, 2022 with the previous PI and IFU to determine if our previous PI and IFU recommendations under OSE RCM 2020-2736 are applicable to the new PI and IFU. Additionally, we reviewed the previously reviewed cartridge container label, MydCombi Product Box carton labeling, replacement cartridge carton labeling, and the Bulk replacement cartridge box carton labeling received on December 28, 2020, to determine if the previous review is reflective of our current thinking as well as to determine if the labels and labeling are acceptable from a medication error perspective.

In the PI we note the Applicant has implemented changes in Section 16. (b) (4) and NDC numbers have been revised; however, we did not identify concerns with the proposed revisions from a medication error perspective.

In the IFU, we note the Applicant has made changes. Specifically, the Applicant has edited the heading “important reminders” to include “cleaning instructions,” additionally the section (b) (4) has been removed.

The IFU, which is considered one part of the user interface, was not assessed under the Human Factors validation study (see Section 3.1 above). Therefore, we are unable to determine if the IFU promotes safe and effective use of the proposed product.

The current proposed PI submitted on November 8, 2022, and the cartridge container label, MydCombi Product Box carton labeling, replacement cartridge carton labeling, and the Bulk replacement cartridge box carton labeling received on December 28, 2020, can be improved from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Eyenovia, Inc.

[g] Roosta, N. Label and Labeling Review for MydCombi (tropicamide and phenylephrine HCl) (NDA 215352). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 12. OSE RCM No.: 2020-2736.

4.3 LABELS AND LABELING RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 5. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – General comment			
1.	It is unclear how many metered doses can be delivered by each cartridge.	Clarifying the number of metered doses that can be delivered per cartridge will help to mitigate the risk of administration or dosing errors.	We recommend the Prescribing Information clarifies the number of doses that cartridge can deliver. Consider including this important information in Sections 2, 3, and 16 of the prescribing information.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. Additionally, the storage statement includes a slash "/."	The lower temperatures in the ranges may be overlooked. Additionally, the slash "/" could be misinterpreted as the number one "1."	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges and removing the slash "/." Additionally, we recommend replacing the hyphen symbol with the intended meaning "to." For example, "15°C to (b) (4)°C (59°F to (b) (4)°F)."

4.4 RECOMMENDATIONS FOR EYENOVIA, INC.

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Cartridge Container Label			
1.	The format for expiration date is presented as MM/YY; however, it is unclear how the month	It is unclear if the month portion will be presented using all numeric characters or alphabetical characters. Presenting the month as	Clarify how you intend to express the month portion of the expiration date. Please note, FDA recommends that the human-readable

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	portion will be presented.	two alphabetical characters does not clearly communicate, for example, whether 'MA' or 'JU' is for the months of March or May and the months of June or July, respectively. A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
2.	The proprietary name is presented in (b) (4) (b) (4)	Typically, methods used to highlight a portion of the name (e.g., Tallman lettering or different font color) are reserved for use when a safety concern has been identified that necessitates additional mitigation strategies.	Consider revising the color of the proprietary name throughout your labeling (b) (4)
3.	The route of administration is missing on the principal display panel (PDP).	Required per 21 CFR 201.100(b)(3).	Add the route of administration statement without the use of abbreviations to the PDP. For example: "For Topical Ophthalmic Use Only"

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The cartridge container label does not state the MydCombi cartridge is intended to be used only with the Optejet base unit.	Clearly stating the intended use of each component of this product could mitigate the risk for product misuse.	Consider adding a statement to the PDP of the cartridge container label, similar to the one in Section 16 of the PI, indicating the cartridge is only to be used with the Optejet dispenser base unit. For example: "Only use the MYDCOMBI cartridge with the MYDCOMBI Optejet Dispenser base."
5.	The intended location of the linear barcode is not specified.	Required per 21 CFR 201.25. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is important safety feature that should be part of the label. Furthermore, we acknowledge that the cartons will include cut-outs to provide a view of the enclosed cartridge cartons' bar code.	Clarify where the linear barcode will appear on the container label. Additionally, clarify where on the carton the barcode would be viewable. Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode as well as in an area where it will not be damaged.
MydCombi Product Box Carton Labeling			
1.	The recommended dosage statement is missing.	Required per 21 CFR 201.55.	Add the recommended dosage statement to the carton. For example: Recommended dosage: See Prescribing Information.
2.	As currently presented, the units of temperature measurement	The lower temperatures in the ranges may be overlooked. Additionally,	We recommend revising the storage statement to include the Centigrade symbol (°C) and

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. Additionally, the storage statement includes a slash "/".	the slash "/" could be misinterpreted as the number one "1".	Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges and removing the slash "/." Additionally, we recommend replacing the hyphen symbol with the intended meaning "to." For example, revise to "15°C to (b)(4)°C (59°F to (b)(4)°F)."
3.	The product identifier is missing.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes The product identifier contains the NDC, serial number, lot, and expiration date.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act-Questions and Answers (June 2021).[h] If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2-D data matrix barcode) and human readable product identifier. Additionally, we recommend ensuring there is sufficient space between the 2D matrix

[h] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			barcode and the existing linear barcode
Replacement Cartridge Box Carton Labeling			
1.	The "Rx Only" statement is missing.	Required per 21 CFR 201.100 (b)(1).	Add the "Rx Only" statement to the replacement carton labeling.
2.	The recommended dosage statement is missing.	Required per 21 CFR 201.55.	Add the recommended dosage statement to the carton. For example: Recommended dosage: See Prescribing Information.
3.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. Additionally, the storage statement includes a slash "/".	The lower temperatures in the ranges may be overlooked. Additionally, the slash "/" could be misinterpreted as the number one "1".	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges and removing the slash "/." Additionally, we recommend replacing the hyphen symbol with the intended meaning "to." For example, revise to "15°C to (b) (4) °C (59°F to (b) (4) °F)."
4.	The route of administration appears to be located on the bottom of the Replacement Cartridge carton labeling.	The route of administration statement is important information that should be prominently displayed on the carton.	Relocate the route of administration statement from the bottom of the replacement cartridge carton labeling.
5.	The product identifier is missing.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes The product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	Identifiers under the Drug Supply Chain Security Act-Questions and Answers (June 2021).[i] If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2-D data matrix barcode) and human readable product identifier. Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode
6.	A warning statement appears to be located on the bottom of the carton labeling and not in a more prominent location.	The product's warning information is important information that should be displayed prominently to mitigate the risk of overlooking.	Relocate the warning statement from the bottom panel of the carton labeling to a more prominent location to decrease the risk of users overlooking this important information.
Bulk Replacement Cartridge Box Carton Labeling			
1.	The "Rx Only" statement is missing.	Required per 21 CFR 201.100 (b)(1).	Add the "Rx Only" statement to the bulk replacement carton labeling.
2.	Based on the image included on the MydCombi carton	An end-user could misinterpret the contents of the carton. Clearly	Revise the image on the carton of five cartridges to show only the cartridge portion, similar to

[i] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	containing five cartridges, it appears the carton may also include an Optejet Base Unit.	outlining the contents within the product's box packaging could minimize the risk of confusion and mitigate the risk of delayed treatment due to lack of clarity.	how the image appears on the carton of 1 cartridge. Additionally, consider specifying that the 1- and 5-count cartons containing only cartridge(s) does not include the base unit. For example, "Optejet base unit not included."
3.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. Additionally, the storage statement includes a slash "/."	The lower temperatures in the ranges may be overlooked. Additionally, the slash "/" could be misinterpreted as the number one "1."	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges and removing the slash "/." Additionally, we recommend replacing the hyphen symbol with the intended meaning "to." For example, revise to "15°C to (b) (4) C (59°F to (b) (4) F)."
4.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act-

Table 6. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		carton) for tracking and tracing purposes The product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	Questions and Answers (June 2021).[j] If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2-D data matrix barcode) and human readable product identifier. Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode

[j] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PREVIOUS DMEPA REVIEWS

APPENDIX A.1 METHODS

On January 5, 2023, we searched L: drive, DARRTS and AIMS using the terms, NDA 215352, MydCombi, phenylephrine and tropicamide to identify reviews previously performed by DMEPA

APPENDIX A.2 RESULTS

Our search identified one previous review[b], and we note our previous recommendations are applicable for the current review.

APPENDIX B. HUMAN FACTORS VALIDATION STUDY RESULT REPORT

The HF study results report can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda215352\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mydriasis\5354-other-stud-rep\tr-17271\tr-17271.pdf

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On December 14, 2022, we issued an information request (IR) to request the following information:
We note you did not include a comprehensive use-related risk analysis (URRA). Please provide your comprehensive use-related risk analysis, you should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

On December 19,2022 The Applicant provided a response to the IR that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda215352\0024\m3\32-body-data\32p-drug-prod\pt-spray-alcami\32p7-cont-closure-sys\qd-17201.pdf

\\CDSESUB1\EVSPROD\nda215352\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mydriasis\5354-other-stud-rep\qd-17201\urra-ufmea.pdf

APPENDIX D. CDRH HUMAN FACTORS CONSULT REVIEW

N/A

APPENDIX E. LABELS AND LABELING

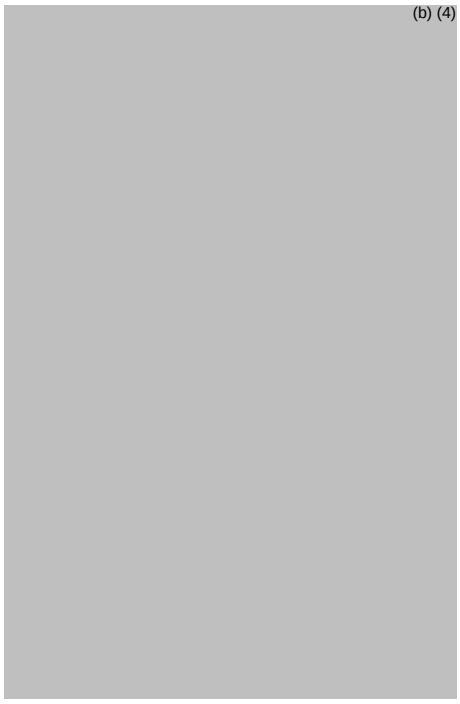
E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following MydCombi labels and labeling submitted by Eyenovia, Inc..

- Cartridge Container label received on December 28, 2020
- MydCombi Product Box labeling received on December 28, 2020
- Replacement Cartridge Carton Labeling received on December 28, 2020
- Bulk Replacement Cartridge Carton Labeling received on December 28, 2020
- Instructions for Use received on November 8, 2022, available from: \\CDSESUB1\EVSPROD\nda215352\0024\m1\us\114-labeling\draft\labeling\instructions-for-use-mydcombi-word.docx
- Prescribing Information (Image not shown) received on November 8, 2022, available from: \\CDSESUB1\EVSPROD\nda215352\0024\m1\us\114-labeling\draft\labeling\draft-labeling-text-pi.docx

E.2 Label and Labeling Images

Cartridge Container label



[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling 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/

SOFANIT N GETAHUN
02/23/2023 12:06:47 PM

VALERIE S VAUGHAN
02/23/2023 12:32:41 PM

OLUWAMUREWA OGUNTIMEIN
02/23/2023 04:32:20 PM

JASON A FLINT
02/24/2023 08:55:40 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 12, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 215352
Product Name and Strength:	MydCombi (Tropicamide and Phenylephrine HCl) ophthalmic spray, 1%/2.5%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eyenovia, Inc.
FDA Received Date:	December 28, 2020
OSE RCM #:	2020-2736
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Human Factors	Jason Flint, MBA, PMP
DMEPA 1 Division Director	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for MydCombi (Tropicamide and Phenylephrine HCl) ophthalmic spray, the Division of Ophthalmology (DO) requested that we review the proposed MydCombi prescribing information (PI), Instructions for Use (IFU), cartridge container label, MydCombi Product Box carton labeling, replacement cartridge carton labeling and the Bulk replacement cartridge box carton labeling for areas of vulnerability that may lead to medication errors.

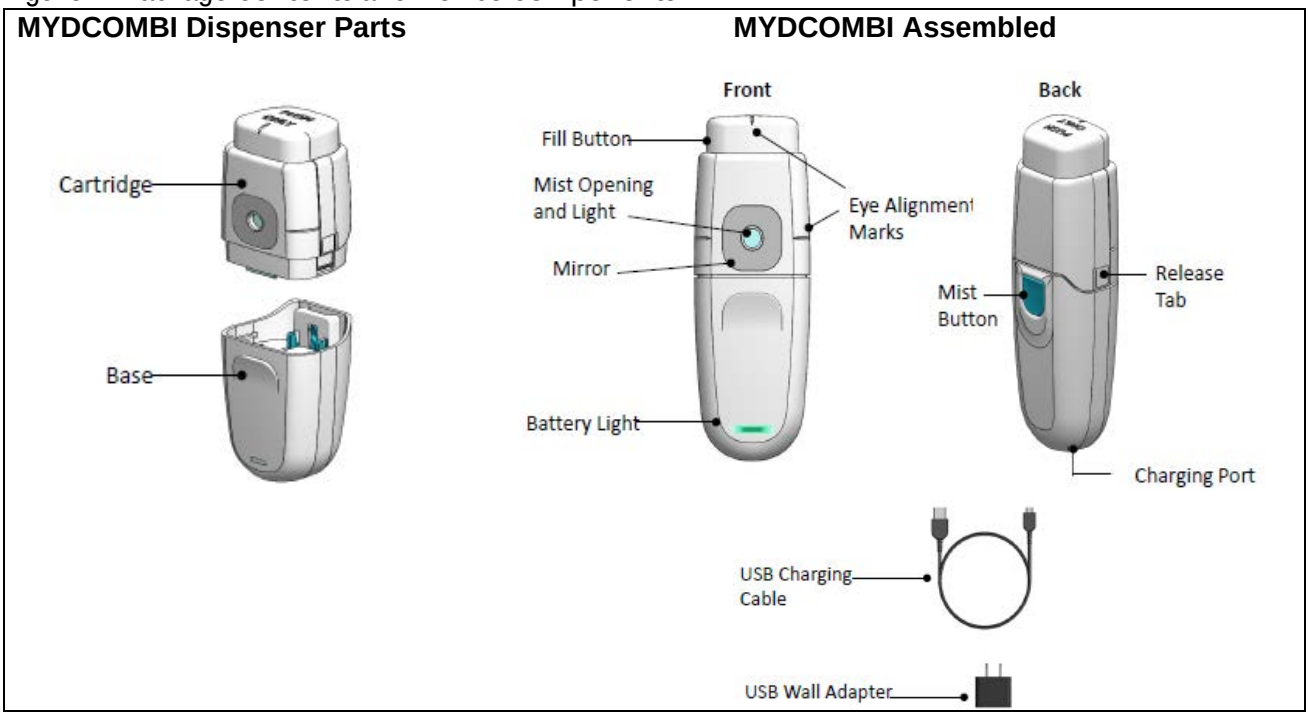
1.1 PRODUCT DESCRIPTION

This is a combination product with proposed mist dispenser device constituent part (drug cartridge that holds the drug solution) packaged with the Optejet™ base that holds electronics. The product is intended for healthcare provider administration only to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired.

The packaging contains:

- The MydCombi Cartridge that contains the drug solution.
- The Optejet Base which supplies power to the dispenser.
- The USB Charging Cable and Wall Adapter to charge the Optejet Base.
- Full Prescribing Information (PI)
- Instructions for use (IFU)

Figure 1. Package Contents and Device Components:



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On December 28, 2020, at the time of submission, NDA 215352 was not deemed to be a combination product; thus, no human factors validation data to demonstrate that the product user interface supports safe and effective use was submitted to the Agency for review.
- On August 23, 2021, the Applicant submitted a study report titled, *Evaluation of the Mydcombi Optject Dispenser Instructions for Use Test Report*. According to the Applicant, this report was submitted in response to a June 29, 2021 request from DO for information regarding the validation of the proposed Mydcombi Instructions for Use in a clinical setting.[a] We note that prior to submission of the study report, the Applicant states that they submitted a study protocol on July 22, 2021 for which DO provided comment via email on July 29, 2021. DMEPA was not aware that a study protocol was submitted; thus, we did not review this study protocol for the Evaluation of the Mydcombi Optejject Dispenser Instructions for Use Test.
- During the review cycle, NDA 215352 was deemed a drug-device combination product.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B -N/A
ISMP Newsletters*	C -N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E -N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

In addition to reviewing the PI and labels and labeling, we conducted a high-level review of the *Evaluation of the Mydcombi Optject Dispenser Instructions for Use Test Report* and found that the study methodology was not adequate to demonstrate that the user interface supports safe

[a] Re: NDA 215352 MydCombi - Tropicamide 1% and Phenylephrine HCl 2.5%" Ophthalmic Spray - Amendment to NDA Application: Instruction for Use (IFU) Study Report. New York (NY): Eyenovia, Inc. 2021 AUG 23. Available from: \\CDSESUB1\evsprod\nda215352\0018\m1\us\12-cover-letters\cover.pdf

and effective use by the intended users, for the intended uses, and in the intended use environments.

The following include some of our methodology concerns:

- There was no use-related risk analysis (URRA) submitted
- There were no critical tasks identified
- The study was designed to validate the instructions for use (IFU), which is only one element of the product user interface.
    - Human factors validation testing should assess all points of interaction between the user and the device, including all elements of the device with which the user interacts.
- The moderator directed each participant to complete each step according to the IFU
    - This is not reflective of an actual use scenario and would be more appropriate for formative human factors work. In a human factors validation study, we would expect that the scenario presented to the user is reflective of what their experience would be in actual use. For example, in actual use, we don't expect that a moderator will be standing by to instruct the user.

These methodology concerns preclude our ability to conduct a thorough review of the study report.

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), Instructions for Use (IFU), cartridge container label, MydCombi Product Box carton labeling, replacement cartridge carton labeling and the Bulk replacement cartridge box carton labeling, may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Eyenovia, Inc. Additionally, during the review cycle, we were notified that Mydcombi has been deemed a combination product. Thus, we provide letter-ready recommendations in Section 5 for Eyenovia, Inc to provide additional human factors validation data to support the safe and effective use of this proposed combination product.

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented in Section 16, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges.

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	first numeric degree measurement in the temperature ranges.		For example, "15°C - (b) (4)C (59°F - (b) (4)°F)".
Instructions for Use (IFU)			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "15°C (b) (4)°C (59°F - (b) (4)°F)".
General Comment			
1.	We note that there was no human factors validation data submitted to support this application. We often have recommendations generated from the HF validation study results that apply to the user interface (for example, IFU, labeling, and device). As such, we may have additional recommendations when HF study results are submitted.		

5 RECOMMENDATIONS FOR EYENOVIA, INC.

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Cartridge Container Label			
1.	The expiration date format on the cartridge container label is presented as MM/YY. .	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. For example, presenting the month as 'MA' or "JU' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and June or July, respectively.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The propriety name is presented in (b) (4)	Typically, methods used to highlight a portion of the name (e.g., tallman lettering or different font color) are reserved for use when a safety concern has been identified that necessitates additional mitigation strategies.	Consider changing the font color of the proprietary name (b) (4) ..
3.	The route of administration is missing on the PDP of the cartridge container label.	Stating the route of administration clearly on the container label will help to minimize the risk of the product being administered via the wrong route and is required per 21 CFR 201.100(b)(3). Additionally, the route of administration is critical information that should appear on the PDP to minimize the risk of this important information being overlooked. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to*	Add the route of administration statement without the use of abbreviations to the PDP of the container label. For example: "For Topical Ophthalmic use only".

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		minimize Medication Errors (April 2013).[b]	
4.	The cartridge container label does not state that the MydCombi cartridge is intended to be used only with the Optejet base unit.	Clearly stating the intended use of each component of this product could mitigate the risk for product misuse.	Consider adding a statement to the PDP of the cartridge container label, similar to the one in Section 16 of the PI, that states the cartridge is only to be used with the Optejet base unit in the accompanied MydCombi Product Box. For example: "Only use the MYDCOMBI cartridge with the MYDCOMBI Optejet® Dispenser base."
5.	The intended location of the linear barcode is not specified.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label.	Add the product's linear barcode to the Cartridge container label as required per 21 CFR 201.25. Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode. Additionally, the barcode should be placed in an area where it will not be damaged.
6.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See

[b] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. The product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[c] Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode.
MydCombi Product Box carton labeling			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "(15°C - (b) (4)°C/ 59°F - (b) (4)°F)".
2.	The MydCombi Product Box carton labeling does not include a contents statement, making it difficult to distinguish the individual	Clearly outlining the contents within the product's box packaging could minimize confusion and mitigate the risk of delayed treatment due to lack of clarity.	Consider adding a contents statement to the side panel of the box carton with the pertinent product information, directly underneath the established name, strength and dosage form.

[c] Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/media/116304/download

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	components within the box.		For example: "Contents: 1 dispenser cartridge 1 Optejet base unit" We recommend incorporating a similar statement on the 1- and 5-count cartridge cartons.
3.	The intended location of the linear barcode is not specified.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label and is required in accordance with 21 CFR 201.25.	Add the product's linear barcode to the MydCombi Product Box as required per 21 CFR 201.25. Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode. Additionally, the barcode should be placed in an area where it will not be damaged.
4.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. The product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[c] Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode.

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	
Replacement Cartridge carton labeling			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "15°C - (b) (4)°C (59°F - (b) (4)°F)".
2.	The route of administration is missing on the Replacement Cartridge carton labeling, where all the pertinent product information is displayed.	Stating the route of administration clearly on the Replacement Cartridge carton labeling, where all the pertinent product information is displayed will help minimize the risk of the product being administered via the wrong route.	Add the route of administration statement without the use of abbreviations to the Replacement Cartridge carton labeling, where all the pertinent product information is displayed, per 21 CFR 201.100(b)(3). For example: "For Topical Ophthalmic use only".
3.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. The product identifier contains the NDC, serial number, lot,	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).Error! Bookmark not defined. Additionally, we recommend ensuring there is sufficient

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	space between the 2D matrix barcode and the existing linear barcode.
4.	The warning statement appears to be located on the bottom of the carton labeling and not in a more prominent location.	The product's warning information is important information that must be easily accessible to the user. If this warning information is not easily accessible to the user, it could be overlooked.	Relocate the warning statements on the bottom panel of the carton labeling to a more prominent location to decrease the risk of users overlooking this important information.
Bulk Replacement Cartridge Box carton labeling			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "15°C - (b)(4)°C (59°F - (b)(4)°F)".
2.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. The	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).Error! Bookmark not defined.

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both can be read correctly upon scanning.	Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode.
3.	The location and format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the location and expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The warning statement appears to be located on	The product's warning information is important	Relocate the warning statements on the bottom

Table 3. Identified Issues and Recommendations for Eyenovia, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the bottom of the carton labeling and not in a more prominent location.	information that must be easily accessible to the user. If this warning information is not easily accessible to the user, it could be overlooked.	panel of the carton labeling to the principal display panel to decrease the risk of users overlooking this important information.

General Recommendation about the User Interface for Eyenovia, Inc.

Mydcombi is a combination product; however we note that you have not submitted human factors validation study data to demonstrate that your user interface supports the safe and effective use of your product by the intended users, for intended uses, and in the intended use environment. As such we request you submit the following to the Agency for review:

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance titled Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications1 for the content of a human factors validation study protocol submission.
The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents[d]:
Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[e]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

[d] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

[e] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for MydCombi that Eyenovia, Inc. submitted on December 28, 2020.

Table 4. Relevant Product Information for MydCombi	
Initial Approval Date	N/A
Active Ingredient	Phenylephrine/tropicamide
Indication	To induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired
Route of Administration	ophthalmic
Dosage Form	ophthalmic spray
Strength	2.5%/1%
Dose and Frequency	In pediatric patients less than 1 year of age, one spray should be administered as required, up to a maximum of 3 sprays per eye per day. In patients 1 year of age or greater, one metered spray to the cornea. (b) (4)
How Supplied	MYDCOMBI is supplied as sterile solution in a 2 mL vial enclosed in a dispenser cartridge. NDC 81046-XXXXX-01. Carton containing one replacement sterile drug cartridge NDC 81046-XXXXX-02. Box containing one carton with one sterile drug cartridge, and one carton with one base unit NDC 81046-XXXX-05. Box containing five cartons, each with one replacement sterile drug cartridge The MYDCOMBI cartridge must be used prior to the expiration date on the cartridge. (b) (4)
Storage	Store at 15°C - (b) (4) °C/59°F (b) (4) °F). (b) (4)

Container Closure	2 mL (b) (4) clear glass vial, (b) (4) and then enclosed into an Opteject Dispenser[f]. (b) (4)

[f] We note that the Opteject Dispenser (cartridge) is supplied pre-assembled with the vial of drug product inside the cartridge.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following MydCombi labels and labeling submitted by Eyenovia, Inc..

- Cartridge container label received on December 28, 2020
- MydCombi Product Box carton labeling received on December 28, 2020
- Replacement Cartridge carton labeling received on December 28, 2020
- Bulk Replacement Cartridge Box carton labeling received on December 28, 2020
- Instructions for Use received on August 23, 2021, available from \\CDSESUB1\evsprod\nda215352\0018\m1\us\114-labeling\draft\labeling\ifu-dispenser.pdf
- Prescribing Information (Image not shown) received on December 28, 2020, available from \\CDSESUB1\evsprod\nda215352\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-pi.pdf

F.2 Label and Labeling Images

Cartridge container label:

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

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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Clinical Inspection Summary

Date	September 13, 2021
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	David Summer, M.D., Medical Officer William Boyd, M.D., Clinical Team Leader Michael Puglisi, Regulatory Health Project Manager Division of Ophthalmology
NDA #	215352
Applicant	Eyenovia, Inc.
Drug	MydCombi (tropicamide 1% and phenylephrine HCl 2.5%) ophthalmic spray
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication(s)	To induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired
Consultation Request Date	February 02, 2021
Summary Goal Date	September 01, 2021; extended to September 28, 2021
Action Goal Date	September 28, 2021
PDUFA Date	October 28, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) were submitted to the Agency in support of this New Drug Application (NDA) 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5%) ophthalmic spray for the proposed indication to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired. Two clinical investigators (CIs): Dr. David Wirta (Site 02 for Study EYN-MYD-TP-31) and Dr. Thomas Walters (Site 04 for Study EYN-MYD-TP-32) were selected for clinical inspections.

The inspections verified the sponsor Eyenovia, Inc. (Eyenovia) submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Studies EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Eyenovia submitted NDA 215352 for MydCombi (tropicamide 1% and phenylephrine HCl 2.5%) ophthalmic spray on 12/28/2020. The proposed indication is to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired. Data from two

Phase 3 clinical studies EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) were submitted to support the approval of the NDA.

Study EYN-MYD-TP-31 (MIST-1)

Study EYN-MYD-TP-31 (MIST-1) was a Phase 3, double-masked, active-controlled, 3-period cross-over superiority study evaluating the safety and efficacy of fixed combination phenylephrine 2.5% (PH) and tropicamide 1% (TR) ophthalmic solution administered with a MicroDose Dispenser (MiDD) for dilation of the pupil.

The study objective was to assess the safety and efficacy of PH-TR ophthalmic solution administered with the MiDD for dilation of the pupil as compared to PH or TR ophthalmic solution alone.

The primary efficacy endpoint was the mean change in pupil diameter at 35 minutes from the time of the first dose versus baseline, as measured by digital pupillometry in highly photopic conditions.

Eligible subjects were equally randomized to six groups and each subject was to receive all 3 study drugs (PH-TR combination, PH and TR) per one of the 6 possible sequences of the three study drug combinations. There were 3 scheduled treatment visits occurring 2-7 days apart. At each treatment visit, 1 of the 3 study drugs according to the assigned study drug sequence was administered to both eyes twice, 5 minutes apart. Efficacy and safety parameters were assessed at specific time intervals.

The study screened a total of 76 subjects, enrolled 70 subjects and randomized 64 subjects in one (1) study site in the US. The first subject was enrolled on November 15, 2018, and the last subject completed the study on December 01, 2018.

Study EYN-MYD-TP-32 (MIST-2)

Study EYN-MYD-TP-32 (MIST-2) was a multi-center, double-masked, placebo-controlled, Phase 3 study of the safety and efficacy of fixed combination phenylephrine 2.5% - tropicamide 1% ophthalmic solution (PH-TR) administered with a MiDD for dilation of the pupil.

The study objective was to assess the safety and efficacy of PH-TR administered with the MiDD for dilation of the pupil as compared to placebo.

The primary efficacy endpoint was the mean change in pupil diameter at 35 minutes from the time of the first dose versus baseline, as measured by digital pupillometry in highly photopic conditions.

Eligible subjects were randomized at a 1:1 ratio to one of the two sequences: ABB and BAA (A was PH-TR and B was the placebo) based on iris color category (dark irides were either black or brown in color, while light irides were all other colors). There were 3 scheduled treatment visits occurring 2-7 days apart. At each visit, the assigned study drug was administered in both eyes twice, 5 minutes apart. Only 1 drug was administered per treatment visit. Efficacy and safety parameters were evaluated at specific time intervals.

The study screened a total of 82 subjects, enrolled 76 subjects and randomized 70 subjects in 2 study sites in the US. The first subject was enrolled on November 19, 2018, and the last subject completed the study on December 21, 2018.

Rationale for Site Selection

Two CIs: Dr. David Wirta (Site 02 for Study EYN-MYD-TP-31) and Dr. Thomas Walters (Site 04 for Study EYN-MYD-TP-32) were requested for inspection in support of the application. These sites were selected based on enrolling a high number of patients to the study treatment arms that may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. David Wirta, M.D., Site 02 for Study EYN-MYD-TP-31(MIST-1)

520 Superior Ave. Suite 235
Newport Beach, CA 92663

This CI was inspected on 08/02-13/2021 as a data audit for Study EYN-MYD-TP-31(MIST-1) under the current NDA, together with Studies OPP-002 and OPP-101 (under NDA 213978), and Study 1883-301-013 (under NDA 214028). This is the 6th inspection for Dr. Wirta. Previous inspections were in 02/2002 with classification of voluntary action indicated (VAI) for informed consent forms (ICFs) failed to include one planned test procedure (pharmacokinetic blood drawn), 08/2004 with no action indicated (NAI), 03/2006 with NAI, 05/2011 with NAI and 11/20/2015 with NAI.

For Study EYN-MYD-TP-31(MIST-1), this is the only clinical study site. The site screened a total of 70 subjects and enrolled 64 subjects, with 62 subjects completed the study. The first subject was enrolled on 11/15/2018 and the last subject completed the study on 12/01/2018. All source records, including eligibility criteria were reviewed for 25 of the 64 enrolled subjects.

Source records reviewed during the inspection included the study protocol and amendment, ICFs with the pediatric assent, documentation of eligibility criteria and enrollment logs, medical records (including visit data, monitoring logs, laboratory tests, ophthalmological exams, AEs, concomitant medication use), the investigational product (IP) accountability records, paper case report forms (CRFs) with electronic CRF (eCRF) entries and audits using the electronic database capture (EDC), protocol deviations and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, ClinicalTrails.gov registration, records retention, staff training logs, financial disclosures and delegation of authority].

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs.

Items discussed for Study EYN-MYD-TP-31(MIST-1) were:

- Protocol deviation: Subject (b) (6) (treatment sequence ABC; A is PH-TR, B is TR and C is PH) had an out of window pupil diameter measurement (6 minutes earlier) on the first day of the study that was not reported as a protocol deviation.
- Incorrect documentations: Subject (b) (6) 35 minutes post dose right eye pupil diameter at Visit 3 was 4.28 in the source documentation but was 4.26 in the eCRF and the data listing. Subject

(b) (6) Visit 1 dose time was 7:26 AM in the source documentation but was 7:25 AM in the eCRF and the data listing.

- Subject (b) (6) (treatment sequence BCA) withdrew the study due to AEs of right eye stye, watery and burning. The AE was not reported in the data listing.

Reviewer's Comments: *Subject (b) (6) AE of right eye stye and irritation should be reported as AEs. The review Division may consider adding the AEs in the safety evaluation.*

In general, this clinical site appeared to be in compliance with Good Clinical Practice (GCP) except the observations noted above. These observations appear unlikely to have significant impacts on the overall efficacy and safety results.

2. Thomas Walters, M.D., Site 04 for Study EYN-MYD-TP-32 (MIST-2)
5717 Balcones Drive
Austin, TX 78731

This CI was inspected on 08/23-25/2021 as a data audit for Study EYN-MYD-TP-32 (MIST-2). This is the 8th inspection for Dr. Walters. Previous inspections were in 03/02/2006 classified as NAI; 11/03/2006 with VAI for protocol violations with four subjects with several out-of-window visit, 11/09/2007 with NAI, 04/19/2012 with VAI for protocol violations with two randomized subjects did not met the inclusion criteria, 02/17/2015 with NAI, 11/03/2015 with NAI and 01/15/2016 with NAI.

For Study EYN-MYD-TP-32 (MIST-2), this site is one of the two study sites. The study site screened a total of 40 subjects, enrolled 36 subjects, with all 36 subjects completed the study. All source records of the 40 screened subjects were reviewed.

Source records reviewed during the inspection included study protocol and amendment, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including monitoring logs, visits data, ophthalmological exams, AEs and concomitant medication use), IP accountability records, paper CRFs with eCRFs data entries through the EDC and signature process, protocol deviations, and related regulatory documents (e.g., IRB approvals and communications, staff training logs, records retention, financial disclosures and delegation of authority).

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs.

At the end of the inspection, a Form 483 (Inspectional Observations) was not issued. There were no discussion items. This clinical site appeared to be in compliance with GCP.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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DO\Reviewer\David Summer
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OSI\DCCE\Division Director\Kassa Ayalew
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OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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