CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216675Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	May 10, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 216675
Product Name, Dosage Form, and Strength:	Miebo (perfluorohexyloctane) ophthalmic solution, 100%
Applicant/Sponsor Name:	Bausch & Lomb Incorporated
TTT ID #:	2022-185-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised trade and professional sample container labels and carton labeling received on May 9, 2023 for Miebo. The Division of Ophthalmology (DO) requested that we review the revised container labels and carton labeling for Miebo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Getahun, S. Label and Labeling Review for Miebo (perfluorohexyloctane). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 14. TTT ID No.: 2022-185.

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/s/

SOFANIT N GETAHUN
05/10/2023 04:56:30 PM

VALERIE S VAUGHAN
05/10/2023 04:59:27 PM

Clinical Inspection Summary

Date	April 26, 2023
From	Lee Pai-Scherf, M.D. Michele Fedowitz, M.D., acting Team Leader Jenn Sellers, M.D. Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE/OSI
To	Shilpa Rose, M.D., Medical Officer Jennifer Harris, M.D., Team Leader Division of Ophthalmology, OND
NDA/BLA #	NDA 216675
Applicant	Bausch & Lomb, Inc.
Drug	Perfluorohexyloctane Ophthalmic Solution, 100% (NOV03)
NME (Yes/No)	Yes
Therapeutic Classification	Semifluorinated alkane
Proposed Indication(s)	Treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD)
Consultation Request Date	August 8, 2022
Summary Goal Date	March 28, 2023 (extension to April 30, 2023)
Action Goal Date	May 30, 2023
PDUFA Date	June 28, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two randomized, double-blind, placebo-controlled trials, Studies NVU-003 and BL-904, were submitted to the Agency in support of New Drug Application (NDA) 216675 for Perfluorohexyloctane Ophthalmic Solution, 100% for the above proposed indication.

Four clinical investigators (CIs), Drs. David Evans (Site # 107) and David Wirta (Site # 101) for Protocol NVU-003; Drs. Bruce Segal (Site # 211) and Fred Kurata (Site # 244) for Protocol BL-904, were inspected.

Although one subject was enrolled at Dr. Wirta's site who met exclusion criteria and there were instances of inadequate record keeping at Dr. Kurata's site, these regulatory deviations did not appear to have significant impact on the efficacy endpoint or safety evaluation of the investigational product (IP). The inspections of the other two CIs revealed no regulatory violations or discrepancies. Based on the results of these inspections, Studies NVU-003 and BL-904 appear to have been conducted adequately and the data generated by the inspected clinical investigators appear acceptable in support of the respective indication proposed in the NDA.

Of note, the inspection results of Dr. Kurata are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, and addendum to this clinical inspection summary will be filed.

II. BACKGROUND

NOV03 (perfluorohexyloctane, 100%) is a sterile ophthalmic solution developed for the treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD). Perfluorohexyloctane forms a monolayer at the air-liquid interface of the tear film which, stabilize the natural tear film and to reduce evaporation. The exact mechanism of action of perfluorohexyloctane in DED is not known.

Data from two randomized, double-blind, placebo control trials, similar in design, NVU-003 and BL-904, were submitted by Bausch & Lomb to support the above indication.

NVU-003 was a phase 3, multi-center, randomized, double-masked, saline-controlled trial to evaluate the effect of NOV03 (100% perfluorohexyloctane) at 4 times daily (QID) dosing regimen on signs and symptoms of DED.

A total of 599 eligible subjects were randomized (304 in the NOV03 arm and 295 in the placebo arm) across 26 investigational sites in the United States. Randomization was stratified by clinical site and dryness score <70 vs 70 (visual analogue scale [VAS]) at baseline, 1:1 to receive either NOV03 (100% perfluorohexyloctane), QID or saline (0.6% sodium chloride solution), QID.

The study has two primary efficacy endpoints, to be tested in the order below using hierarchical fixed sequence testing:

1. Change from baseline (CFB) in total Corneal Fluorescein Staining (tCFS) (National Eye Institute [NEI] scale) at Day 57

2. CFB of Dryness Score (VAS Severity of Dryness) at Day 5

Secondary efficacy endpoints are CFB of Dryness Score (VAS) at day 15; CFB in total Corneal Fluorescein Staining (tCFS) (NEI scale) at day 15, CFB of VAS burning/stinging at day 57, and CFB in central Corneal Fluorescein Staining (cCFS) (NEI scale) at Day 57.

Study BL-094 was similar to NVU-003 in design, study population, study objectives, IP administration, efficacy, and safety endpoints. Data from a total of 622 randomized subjects (312 to the NOV03 arm and 310 to the placebo arm) enrolled at 42 clinical investigational sites across the United States were submitted to support the application.

Four clinical investigators, Drs. David Evans (site # 107 for NVU-003), Bruce Segal (site # 211 for BL-904), David Wirta (site # 101 for NVU-003), and Fred Kurata (Site # 244 for BL-94), were selected for inspection by DO and OSI, taking into consideration the total number of subjects enrolled and safety and efficacy parameters.

III. RESULTS (by site):

1. **Dr. David G. Evans (**Site # 107**)**
   Total Eye Care, PA
   6060 Primacy Parkway, Suite 200
   Memphis, TN 38119

   Inspection dates: 12/05 – 12/09/2022

   Dr. Evans was inspected as a surveillance inspection for Study NVU-003. This was the third inspection for Dr. Evans. The two prior inspections occurred on 03/15/2018 and 09/18/2003, both received No Action Indicated (NAI) classification.

   A total of 69 subjects were screened and consented with 9 screen failures and 60 subjects enrolled at the site. At the time of the inspection, 59 subjects had completed the study and one subject had discontinued from study. There were no study-related deaths reported at the site.

   Source documents for 25 subjects were reviewed and compared with the line listings from the NDA and the Electronic Data Capture (EDC). The inspection covered subject's eligibility records, adverse event reports, primary efficacy endpoint data, informed consent forms, protocol deviations, concomitant medications, subjects' diaries, and investigational product administration records. All reviewed subjects met protocol specified inclusion and exclusion criteria and signed informed consent prior to study activities. There was no underreporting of AEs or significant protocol deviations.

   Source data for the primary and secondary endpoints were reviewed and compared with the line listings and the EDC. There were no discrepancies in the primary endpoint or key secondary endpoints.

   Additional study related records reviewed include IRB and monitor correspondence, training records, investigational drug accountability (storage and shipment), and study worksheets. No discrepancies were noted.

   The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Evans at the conclusion of the inspection.

2. **Bruce Segal, M.D.** (Site # 21)
   5258 Linton Blvd # 302
   Delray Beach, FL 33484

   Inspection dates: 11/28 – 11/29/2022

   Dr. Segal was inspected as a surveillance inspection for Study BL-904. This was the first inspection for Dr. Segal.

   A total of 59 subjects were screened and 40 subjects were enrolled at the site. At the time of the inspection, 33 subjects had completed the study and 7 subject had discontinued from study (3 subjects withdrew consent, 3 had protocol violations, and 1 subject was withdrawn for non-compliance). There were no SAEs or study-related deaths reported at the site.

   Source documents for all 40 subjects enrolled at the site were reviewed and compared to data listings submitted to the NDA. Documents reviewed included demographic forms, medical intake forms, visit specific tasks/notes, adverse events forms, concomitant medication logs, subject dosing diaries, laboratory results, and source documents related to the primary and secondary endpoints. All subjects met protocol specified inclusion and exclusion criteria and had signed informed consent prior to study activities. AEs were reported accurately and there were no SAEs.

   Source data for the primary and secondary endpoints were reviewed and compared with the line listings submitted to the NDA for 40 of 40 subjects enrolled at the site and there were no discrepancies.

   Additional study related documents reviewed include, but were not limited to financial disclosure forms, IRB documents, investigational drug accountability, monitoring records, and site staff training records.

   The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Segal at the conclusion of the inspection.

3. **David Wirta, M.D.** (Site # 101)
   Eye Research Foundation
   520 Superior Ave, Suite 235
   Newport Beach, CA 92663

   Inspection dates: 04/03 – 04/06/2023

   Dr. Wirta was inspected as a surveillance inspection for Study NVU-003. Dr. Wirta was previously inspected on 05/19/2021 and 11/20/2015, both with inspection

classifications of no action indicated (NAI), and on (b) (6), with an inspection classification of voluntary action indicated (VAI) for inadequate record keeping. Specifically, he failed to report concomitant medications (please refer to Reviewer's Comments below).

The site screened a total of 70 subjects and 60 subjects were enrolled into the NVU-003 trial. A total of 58 of the 60 subjects completed the study. At the time of the inspection, 58 subjects had completed the study and 2 subject had discontinued due to relocation.

Source records for all 60 subjects enrolled at the site were reviewed for eligibility, consent, primary efficacy endpoint and adverse event reporting. Source documents for 15 subjects were reviewed in more detail for secondary endpoints, concomitant medications, office visit activities and patient diary completion. All subjects signed the informed consent and the primary and secondary efficacy variables reviewed were consistent with the data provided to the NDA. AEs were reported accurately and there were no SAEs.

The following unreported protocol deviation was observed:

Subject # (b) (6) was enrolled in NVU-003 but was ineligible due to simultaneous participation at another research study (Study (b) (6)). Specifically, the subject was enrolled into Study NVU-003 on (b) (6), but records indicate that the subject was participating in Study (b) (6) until (b) (6), meeting exclusion criterion #26 (currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days of Visit).

During the (b) (6) inspection, Dr. Wirta was issued a Form FDA 483 for inadequate recordkeeping of Study (b) (6); he enrolled and randomized subjects into new investigational drug studies but failed to report in the eCRFs (electronic case report forms) the investigational drugs taken by the subjects in these studies as concomitant medications.

Reviewers comment: The co-enrollment into two clinical studies for Subject # (b) (6) was previously discovered during the (b) (6) FDA inspection for NDA (b) (6) of Study (b) (6). Dr. Wirta notified the Sponsor in (b) (6) of the protocol deviation for Subject # (b) (6) in the current study (Study NVU-003), but it was not recorded in the data submitted to FDA because the database had been locked April 2021, prior to the Sponsor's notification. Dr. Wirta implemented corrective and preventive actions in 2021 that were reviewed and found to be acceptable to address the regulatory violations in both studies. Subject # (b) (6) did not experience adverse events as a result of the violation. There is no evidence of subject harm related to the finding.

Additional study related documents reviewed include, but were not limited to, financial disclosure forms, IRB approvals, treatment/dispensing of the investigational product, accountability, monitoring and reporting, and information on staff training.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Wirta at the conclusion of the inspection.

4. **Fred Kurata, M.D.** (Site # 244)
Premiere Practice Management
420 E. 3rd St, Suite 603
Los Angeles, CA 90013

Inspection dates: 03/27 – 03/30/2023

The official establishment inspection report (EIR) is pending. The review below is based on the summary close out email and communications with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.

Dr. Kurata was inspected as a surveillance inspection for Study BL-904. This was the first FDA inspection of Dr. Kurata.

A total of 90 subjects were screened and consented with and 70 subjects enrolled at the site. Source documents for all subjects were reviewed and compared with the line listings from the NDA. The inspection covered subject's eligibility records, adverse event reports, informed consent forms. All reviewed subjects met protocol specified inclusion and exclusion criteria and signed informed consent prior to study activities. There was no underreporting of AEs or significant protocol deviations.

Source records for the primary endpoint for all subjects enrolled and the secondary endpoints for a subset of subjects were reviewed and compared with the data submitted to the NDA. No discrepancies in the primary endpoint or key secondary endpoints variables reviewed were observed.

Dr. Kurata was issued a Form FDA 483 at the close of the inspection citing inadequate record keeping for the investigation. Source documents indicated that the CI performed various ophthalmic exams for different subjects on the same day and at the same time, as shown in the following table:

Subject	Ophthalmic Exam	Date Performed	Time Performed
(b) (6)	Intraocular Pressure	19-Aug-21	(b) (6)
	Meibomian Gland Assessment	19-Aug-21	
	Slit Lamp Biomicroscopy	19-Aug-21	
	Corneal Fluorescein Staining	19-Aug-21	

(b) (6)			(b) (6)
	Intraocular Pressure	19-Aug-21	
	Slit Lamp Biomicroscopy	19-Aug-21	
	Intraocular Pressure	19-Aug-21	
	Meibomian Gland Assessment	19-Aug-21	
	Intraocular Pressure	19-Aug-21	
	Intraocular Pressure	19-Aug-21	
	Dilated Fundoscopy	20-Aug-21	
	Intraocular Pressure	20-Aug-21	
	Slit Lamp Biomicroscopy	19-Aug-21	
	Dilated Fundoscopy	19-Aug-21	
	Meibomian Gland Assessment	19-Aug-21	
	Dilated Fundoscopy	19-Aug-21	
	Slit Lamp Biomicroscopy	19-Aug-21	
	Dilated Fundoscopy	19-Aug-21	
	Corneal Fluorescein Staining	19-Aug-21	
	Meibomian Gland Assessment	19-Aug-21	
	Dilated Fundoscopy	19-Aug-21	
	Slit Lamp Biomicroscopy	19-Aug-21	
	Tear Film Breakup Time	19-Aug-21	
	Corneal Fluorescein Staining	19-Aug-21	

Reviewer's Comments: Per discussion with the review division on 03/30/2023, the above eye examination can be performed quickly, in a matter of seconds, however the site should improve documentation and record the time with at least one minute difference between each examination.

In response to the 483, Dr. Kurata subsequently provided a Corrective and Preventive Action Plan, which was reviewed and found to be adequate.

Notwithstanding the documentation issue described above, data generated by Dr. Kurata appear to be acceptable in support of the NDA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Michele Fedowitz, M.D.
Acting Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Jenn Sellers, MD PhD
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
DARRTS: NDA 216675
Review Division /Project Manager/Jacquelyn Smith
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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JENN W SELLERS
04/26/2023 03:45:34 PM

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

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

Memorandum

Date: April 20, 2023

To: Jacquelyn Smith, Senior Regulatory 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: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for MIEBO (perfluorohexyloctane ophthalmic solution), 100%, for topical ophthalmic use.

NDA: 216675

Background:
In response to the Division of Regulatory Operations for Specialty Medicine (DROSM) consult request dated August 22, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for MIEBO (perfluorohexyloctane ophthalmic solution), 100%, for topical ophthalmic use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 10, 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 April 10, 2023, and we do not have any comments at this time.

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

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CARRIE A NEWCOMER
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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:	December 14, 2022
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 216675
Product Name and Strength:	Miebo (perfluorohexyloctane ophthalmic solution), 100%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bausch & Lomb Incorporated
FDA Received Date:	June 28, 2022,
TTT ID #:	2022-185
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 REASON FOR REVIEW

As part of the approval process for Miebo (perfluorohexyloctane ophthalmic solution), the Division of Ophthalmology (DO) requested that we review the proposed Miebo prescribing information (PI), container label, carton labeling, professional sample container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

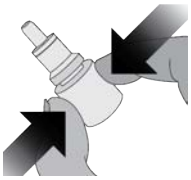
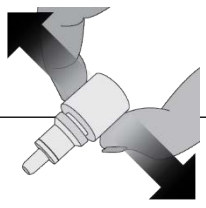
Material Reviewed	Appendix Section (For Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Clinical Trial Protocol NVU-003	E
Labels and Labeling	F

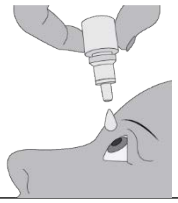
N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION

Our preliminary review of the administration instructions in Section 2.1 of the Prescribing Information (PI), noted that Steps 2 and 3 (see Table 2) differ in administration steps in comparison to administration of other topical ophthalmic solutions supplied in eye dropper bottles.

Table 2. Proposed Administration Instructions

Step 1. Remove the cap from eye drop bottle.
 **Step 2.** Holding the bottle upright, gently squeeze the bottle.


Step 3. While squeezing, turn the bottle upside down and release the pressure [drawing air into the bottle].
 **Step 4.** Keeping the bottle upside down, place the bottle above your eye and squeeze it again to release a drop into your eye. Repeat steps 1 – 4 for the second affected eye.

To determine if Steps 2 and 3 are critical to the use of the proposed eye dropper bottle, we reviewed the administration instructions included in Appendix 2 of Clinical Trial Protocol NVU-003 (see Appendix E) that our clinical reviewer colleague shared with us and note that protocol NVU-003 includes additional instruction to clarify that the eye dropper bottle can be used as one would customarily use an eye dropper bottle that is, omitting steps 2 and 3 shown above and performing step 4 after opening the bottle.

On a separate note, our clinical reviewer colleague also indicated, *"there do not appear to be any dosing errors in Studies NVU003 and BL904 based on administration instructions. No protocol deviations were noted or adverse events secondary to IFU and bottle use."*

As such, based on the available information, we determined Steps 2 and 3, while they may be preferred, are not critical to the use of the proposed eye dropper bottle.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI) container label, carton labeling, professional sample container label and 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 Bausch & Lomb Incorporated.

5 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 3. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	We note that the placeholder, "TRADENAME" is	The proposed proprietary name, Miebo, was found conditionally acceptable on	Replace the placeholder, "TRADENAME," with the

Table 3. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included throughout the PI.	August 30, 2022[a]. The proprietary name, "Miebo," should be used throughout the PI.	conditionally acceptable proprietary name, "Miebo."
2.	As currently presented, we note throughout the PI, container label and carton labeling the (b) (4)	We confirmed with our Office of Pharmaceutical Quality colleagues (b) (4)	We recommend revising such (b) (4) "Miebo (perfluorohexyloctane ophthalmic solution), (b) (4)
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristic can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).	Include the description of identifying characteristic of the dosage form, such as color and clarity in accordance with 21 CFR 201.57(c)(4(ii). Similar to what is stated in *Section 11, Description*, "Clear and colorless liquid."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented the appropriate information to facilitate identification of the	A description of identifying characteristic can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Include the description of identifying characteristic of the dosage form, such as color and clarity in accordance with 21 CFR 201.57(c)(17)(iii). Similar to

[a] Chan, I. Proprietary Name Request Conditionally Acceptable for Miebo. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 30. NDA 216675.

Table 3. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	dosage form is not included.		what is stated in *Section 11, Description*, "Clear and colorless liquid."

6 RECOMMENDATIONS FOR BAUSCH & LOMB INCORPORATED

Table 4. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, we note on the container label and carton labeling (b) (4)	(b) (4)	We recommend revising such (b) (4) "Miebo (perfluorohexyloctane ophthalmic solution), (b) (4)
2.	The format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the 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

Table 4. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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.
3.	As currently presented, the terminology "(b) (4) " is inconsistent with the terminology used in the Prescribing Information Dosage and Administration section.	The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion.	To ensure consistency with the Prescribing Information, we recommend revising the dosage statement, (b) (4) " to read "Dosage: See Prescribing Information."
Carton Labeling			
1.	As currently presented, the proposed carton labeling and professional sample carton labeling denote an "Area for Lot, Exp. and Serialization." However, the intended location of the machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and	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* (July 2021).[b] If you determine that the product identifier requirements apply to your product's labeling, we request

[b] 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 4. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		machine-readable (2D data matrix barcode) format.	you add a place holder to the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Miebo that Bausch & Lomb Incorporated submitted on June 28, 2022.

Table 5. Relevant Product Information for Miebo	
Initial Approval Date	N/A
Active Ingredient	Perfluorohexyloctane
Indication	Treatment of signs and symptoms of dry eye disease associated with meibomian gland dysfunction.
Route of Administration	Topical ophthalmic
Dosage Form	Ophthalmic solution
Strength	100%
Dose and Frequency	Instill one drop four times daily into each eye.
How Supplied	3 mL fill in a 5 mL container NDC 24208-377-05
Storage	20°C to 25°C (68°F to 77°F); (b) (4) After opening can be used until the expiration on the bottle.
Container Closure	Polypropylene bottles with dropper tips and screw caps.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 26, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, perfluorohexyloctane and NDA 216675. Our search did not identify any previous reviews.

APPENDIX E. Clinical Trial Protocol NVU-003

Clinical Trial Protocol NVU-003

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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,[c] along with postmarket medication error data, we reviewed the following Miebo labels and labeling submitted by Bausch & Lomb Incorporated.

- Container label received on June 28, 2022
- Carton labeling received on June 28, 2022
- Professional Sample Container label received on June 28, 2022
- Professional Sample Carton labeling received on June 28, 2022
- Prescribing Information (Image not shown) received on June 28, 2022, available from:
    - Annotated version: \\CDSESUB1\evsprod\nda216675\0001\m1\us\annotated-draft-labeling-text.pdf
    - Clean version: \\CDSESUB1\evsprod\nda216675\0001\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label

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

Carton labeling

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

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/s/

SOFANIT N GETAHUN
12/14/2022 01:53:27 PM

VALERIE S VAUGHAN
12/15/2022 10:12:23 AM