CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761355Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME MEMORANDUM

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:	August 15, 2023
Application Type and Number:	BLA 761355
Product Name and Strength:	Eylea HD (aflibercept) injection, 8 mg/0.07 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc. (Regeneron)
PNR ID #:	2023-1044725222
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Director:	Mishale Mistry, PharmD, MPH

1 INTRODUCTION

This memorandum is to reassess the proposed proprietary name, Eylea HD, which was found conditionally acceptable under BLA 761355 on March 27, 2023.[a] However, BLA 761355 received a complete response (CR) on June 27, 2023, due to facility issues.[b] Thus, Regeneron responded to the CR and submitted the name, Eylea HD, under BLA 761355 for review on July 3, 2023. We note that all product characteristics remain the same.

2 METHODS AND DISCUSSION

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Eylea HD would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Eylea HD. The Division of Ophthalmology (DO) did not comment on the findings of OPDP's assessment for Eylea HD.

2.2 SAFETY ASSESSMENT

For re-assessment of the proposed proprietary name, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. Our reassessment did not change our conclusion regarding the previously identified names of concern. Additionally, we searched the United States Adopted Name (USAN) stem list to determine if the proposed proprietary name contains any USAN stems as of the last USAN updates. The July 7, 2023 search of USAN stems did not find any USAN stems in the proposed proprietary name, Eylea HD.

2.3 COMMUNICATION OF DMEPA'S DETERMINATION

On August 15, 2023, we communicated our determination to the Division of Ophthalmology (DO).

3 CONCLUSION

Our re-assessment did not identify any names that represent a potential source of drug name confusion. Therefore, we maintain that the proposed proprietary name, Eylea HD, is conditionally acceptable.

If you have any questions or need clarifications, please contact Oyinlola Fashina, OSE project manager, at 301-796-4446.

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[a] Birkemeier D. Proprietary Name Review for Eylea HD (BLA 761355). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 27. PNR ID No. 2022-1044724913.

[b] Puglisi M. Complete Response for Eylea HD (BLA 761355). Silver Spring (MD); FDA, CDER, OND, DAAP (US); 2023 JUN 27. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806d96de

3.1 COMMENTS TO REGENERON PHARMACEUTICALS, INC.

We have completed our review of the proposed proprietary name, Eylea HD, and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your submission, received on July 3, 2023, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)***
   USAN Stems List contains all the recognized USAN stems.

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/s/

DAMON A BIRKEMEIER
08/15/2023 04:06:06 PM

VALERIE S VAUGHAN
08/15/2023 04:09:03 PM

MISHALE P MISTRY
08/15/2023 04:28:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From:

Carlos M Mena-Grillasca, BS Pharm
Biologics Suffix Specialist, DMAMES
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Through:

Mishale Mistry, PharmD, MPH
Director, Division of Medication Error Prevention and Analysis I (DMEPA 1)
Office of Medication Error Prevention and Risk Management
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Gerald Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Subject: Evaluation of the nonproprietary name for BLA 761355

Regeneron Pharmaceuticals, Inc. submitted a new Biologics License Application (BLA 761355) pursuant to Section 351(a) of the Public Health Service Act, for a new formulation and strength of a currently approved biological product: Eylea (aflibercept) (BLA 125387). Regeneron is the license holder for BLA 125387 and the applicant for BLA 761355.

Eylea (aflibercept) is a vascular endothelial growth factor (VEGF) inhibitor and is currently approved for intravitreal injection for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and retinopathy of prematurity (ROP). Eylea is currently supplied as a single-dose prefilled syringe (2 mg/0.05 mL) and single-dose vial (2 mg/0.05 mL).

The new formulation in BLA 761355 contains the same drug substance (aflibercept) formulated at a higher concentration, resulting in a higher strength (8 mg/0.07 mL), intended for the same indications of Neovascular (wet) Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) (not for RVO and ROP), and same route of administration (intravitreal) and dosage form (injection). The higher dose will result in the same or reduced frequency of administration as the currently approved product. See Appendix 1 - Product Characteristics Comparison Table for more information.

Per the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, "A change to an approved product based on chemistry, manufacturing, or controls data and bioequivalence, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients) can be submitted as a supplement to an approved application. Such change would not ordinarily warrant a new original application unless it changes the dosage form or route of administration)." In fact, we note that the pre-BLA meeting minutes[a] indicate that "The Agency clarified that it is acceptable to submit the application for the 8 mg product as a new BLA or as an efficacy supplement to the existing BLA for Eylea."

FDA issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017, stating the Agency's intention to designate proper names that include four-letter

[a] Puglisi, M.J. Type B, Pre-BLA Meeting Minutes for Eylea (aflibercept). Silver Spring (MD): FDA, CDER, OND, DO (US); 22 Oct 14. IND 012462

distinguishing suffixes for biological products[a]. This 351(a) application (BLA 761355) is within the scope of this naming guidance.

The currently approved formulation for Regeneron's BLA 125387 is also within the scope of the naming guidance. However, the draft updated guidance, issued in March 2019, addresses nonproprietary names of biological products licensed under section 351(a) that do not include an FDA-designated suffix[b]. The updated guidance, if finalized, will explain that FDA does not expect the nonproprietary names of such products to be revised in order to accomplish the objectives of the naming convention described in the January 2017 final guidance for industry.

We carefully considered whether the nonproprietary name of the new proposed formulation in BLA 761355 should include a suffix or whether the proper name considerations for this product warrant departing from the January 2017 final guidance. Among the factors we have considered are the following:

1. The drug substance (DS) in the approved formulation (BLA 125387) and the proposed formulation (BLA 761355) are essentially unchanged with respect to product quality attributes (identity, purity, etc.). The main difference between the formulations is an increased concentration resulting in a higher strength (2 mg/0.05 mL vs. 8 mg/0.07 mL) and higher dose (2 mg vs. 8 mg)[c].
2. We note that all other product characteristics are the same or similar: indications (AMD, DME, RVO, DR, and ROP vs. AMD, DME, DR), formulation (liquid), dosage form (injection), route of administration (intravitreal), and frequency of administration (every 4 weeks or every 8 weeks or every 12 weeks vs. every 4 weeks or every 8 – 16 weeks). See Appendix 1.
3. The drug substance in BLA 761355 is the same as the drug substance in BLA 125387, and both BLAs propose a liquid formulation in single-dose prefilled syringe or vial.
4. Considering that BLA 125387 and BLA 761355 share the same drug substance and the formulation similarities, no significant differences in immunogenicity profiles is expected.

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[a] Available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf (hereafter "naming guidance").

[b] Available at https://www.fda.gov/media/121316/download

(b) (4)

5. As noted above, the proposed BLA 761355 could have been managed under a supplement to the current BLA 125387, which would not have resulted in a change to the proper name under the approach to nonproprietary naming described int the final guidance.
6. Regeneron is proposing to have a separate U.S. prescribing information (USPI) that would include the proposed product and proposed indications. Regeneron is proposing to have a different proprietary name for the proposed formulation, Eylea HD, which was found conditionally acceptable by DMEPA 1[a]. The naming convention of using a different proprietary name for the same product that has different formulation/ indications has been found acceptable by the Agency.

As noted in the final Nonproprietary Naming of Biological Products guidance, distinguishing nonproprietary names will facilitate pharmacovigilance when other means to track a specific dispensed product are not readily accessible or available; facilitate accurate identification of these biological products by health care practitioners and patients; and help prevent inadvertent substitution that may lead to medication errors. As the guidance explains, a distinguishing suffix supports the tracking of product-specific events over time, our ability to track adverse events to a specific manufacturer (and as appropriate, to a manufacturing lot or manufacturing site for a particular biological product), and our ability to detect safety signals throughout the life cycle of a product so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address a problem. As noted above, the drug substance proposed in this submission, aflibercept, is essentially unchanged with respect to product quality attributes. Also, as noted above, Regeneron is the applicant for BLA 125387 and BLA 761355.

Given the above factors, a different nonproprietary name for BLA 761355 would not be designated in this particular case. The addition of a suffix to the nonproprietary name for BLA 761355 could create confusion and would not further the goals of the naming convention.

This memorandum documents the justification for and supervisory concurrence with the decision to depart from the recommendations in the January 2017 final Nonproprietary Naming of Biological Products guidance in approving the same nonproprietary name for BLA 761355[b]. We based this

[a] Birkemeier, D. Proprietary Name Review for Eylea HD (BLA 761355). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 27 Mar 2023. Nexus PNR ID 2022-1044724913.

[b] See 21 C.F.R. § 10.115(d)(3) "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

determination upon consideration of all the factors outlined above. If any of the factors enumerated above were to change, we may reconsider the appropriate proper name for this BLA.

The following will be communicated to Regeneron in an advice letter.

Comments for Regeneron Pharmaceuticals, Inc. for IND 012462 and BLA 761355:

We have determined that aflibercept will be the proper name designated in the license, should your 351(a) BLA be approved during this review cycle.

We note that you submitted proposed nonproprietary name suffixes for our evaluation. However, considering that per the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, "A change to an approved product based on chemistry, manufacturing, or controls data and bioequivalence, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients) can be submitted as a supplement to an approved application. Such change would not ordinarily warrant a new original application unless it changes the dosage form or route of administration." In addition, the pre-BLA meeting minutes indicate that "The Agency clarified that it is acceptable to submit the application for the 8 mg product as a new BLA or as an efficacy supplement to the existing BLA for Eylea". Therefore, if the application for the 8 mg product was submitted as an efficacy supplement to the existing BLA 012462 for Eylea, there would not be a change to the proper name under the approach to nonproprietary naming described in the final guidance.

Finally, since the drug substance, aflibercept, is essentially the same between the products with regards to product quality attributes (e.g., identity, purity, etc.), the addition of a suffix to the nonproprietary name for BLA 761355 could create confusion and would not further the goals of the naming convention.

Appendix 1

Product Characteristics Comparison for Eylea vs. Eylea HD		
Product Name	Eylea	Eylea HD
Nonproprietary Name	aflibercept	aflibercept
Indication	• Neovascular (wet) Age-Related Macular Degeneration (AMD) • Macular Edema following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) • Retinopathy of Prematurity (ROP)	• Neovascular (wet) Age-Related Macular Degeneration (AMD) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Route of Administration	intravitreal	
Dosage Form	injection	
Strength	2 mg/0.05 mL	8 mg/0.07 mL
Dose and Frequency	AMD: 2 mg every 4 weeks for the first 3 months, followed by 2 mg once every 8 weeks (some patients may be dosed every 4 weeks or every 12 weeks) DME and DR: 2 mg every 4 weeks for the first 5 injections, followed by 2 mg every 8 weeks.	(b) (4)
How Supplied	Single-dose vial Single-dose prefilled syringe	Single-dose vial
Storage	Refrigerate at 2° C to 8° C (36° F to 46° F).	Refrigerate at 2° C to 8° C (36° F to 46° F).

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/s/

CARLOS M MENA-GRILLASCA
05/11/2023 10:39:11 AM

IRENE Z CHAN on behalf of MISHALE P MISTRY
05/11/2023 10:59:30 AM

PROPRIETARY NAME 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:	March 27, 2023
Application Type and Number:	BLA 761355
Product Name and Strength:	Eylea HD (aflibercept-xxxx)[a] injection, 8 mg/0.07 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc. (Regeneron)
PNR ID #:	2022-1044724913
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Director:	Mishale Mistry, PharmD, MPH

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder adalimumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Eylea HD, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. Regeneron submitted an external name study, conducted by [redacted] (b) (4) for this proposed proprietary name.

1.1 REGULATORY HISTORY

On May 25, 2011, and November 4, 2011, we found the name, Eylea, acceptable and Eylea was approved on November 18, 2011, under BLA 125387.[b,c]

Regeneron submitted the name, Eylea HD, for review on December 27, 2022, noting that "[*Eylea HD] sharing identical drug substance [aflibercept], aflibercept 8 mg intravitreal [Eylea HD] is a distinctly different drug product from aflibercept 2 mg intravitreal [Eylea] in both strength and formulation.*"

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on December 27, 2022 and from FDALabel (for the approved product, Eylea).[d]

Table 1. Relevant Product Information for Eylea HD (aflibercept-xxxx) and Eylea (aflibercept)

Product Name	**Eylea HD** (proposed)	**Eylea**
Initial Approval Date	N/A	November 18, 2011
Application Number	BLA 761355	BLA 125387
Intended Pronunciation	eye lee' ah aych dee	Eye lee' ah
Non-proprietary name	aflibercept-xxxx	aflibercept
Indication	• Neovascular (Wet) Age-related Macular Degeneration (nAMD) • Diabetic Macular Edema (DME)	• Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)

[b] Fava W. Proprietary Name Review for Eylea (aflibercept) (IND 012462 and BLA 125387). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAY 25. OSE RCM No. 2010-1480 and 2011-538.

[c] Fava W. Proprietary Name Review for Eylea (aflibercept) (BLA 125387). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 NOV 4. OSE RCM No. 2011-3160.

[d] Eylea [Prescribing Information]. FDALabel. U.S. Food and Drug Administration. February 2023. [cited 2023 MAR 02]. Available from: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/f96cfd69-da34-41ee-90a9-610a4655cd1c/spl-doc?hl=eylea

	• Diabetic Retinopathy (DR)	• Macular Edema Following Retinal Vein Occlusion (RVO) • Retinopathy of Prematurity (ROP)
Route of Administration	intravitreal injection	
Dosage Form	injection	
Strength	8 mg/0.07 mL	2 mg/0.05 mL
Dose and Frequency	(b) (4)	• nAMD: 2 mg administered every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg administered every 8 weeks (2 months). Some patients may need every 4-week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. • DME, DR: 2 mg administered every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg administered every 8 weeks (2 months). Some patients may need every 4-week (monthly) dosing after the first 20 weeks (5 months). • RVO: 2 mg administered every 4 weeks (approximately every 25 days, monthly)

		• ROP: 0.4 mg administered as a single dose. Injection may be repeated, the treatment interval between doses injected into the same eye should be at least 10 days.
How Supplied	• 8 mg/0.07 mL single-dose glass vial • 8 mg/0.07 mL single-dose glass vial kit	• 2 mg/0.05 mL single-dose prefilled syringe • 2 mg/0.05 mL single dose vial kit
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze.	

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Eylea HD.

2.1 MISBRANDING ASSESSMENT

During the initial steps of the proprietary name review process, the Office of Prescription Drug Promotion (OPDP) did not recommend the use of the proposed proprietary name, Eylea HD, because it would misbrand the proposed product. OPDP provided the following statement:

> *OPDP objects to the proposed proprietary name, "Eylea HD" because it creates a misleading impression regarding the efficacy of the drug. The intended pronunciation of "Eylea HD" is "Eye lee' ah aych dee." The proposed portion of the proprietary name, "HD," is an acronym commonly interpreted as, "high definition." High definition can be defined as "a system for screen display of images that are sharper and more detailed than normal, having many more than the standard number of scanning lines per frame" (https://www.dictionary.com/browse/high-definition; accessed 1/12/2022). The proposed indication for this drug is for the treatment of neovascular (wet) age-related macular degeneration, diabetic macular edema and diabetic retinopathy. According to the Request for Proprietary Name Review submitted by Regeneron, the "HD" is meant to denote "high dose." However, the acronym "HD" is likely to evoke the term "high definition." Therefore, in the context of the proposed indications for degenerative retinal diseases associated with progressive vision loss, the evocation of the term "high definition" misleadingly implies that the drug can improve or restore a patient's vision to the extent that they can view images more sharply and, in more detail than normal, when this is not the case. Because the proposed portion of the proprietary name, "HD," overstates the efficacy of the drug, it would be misleading. Please note that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A proprietary name or non-proprietary name suffix, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.*

The Division of Ophthalmology (DO) disagreed with OPDP's initial assessment and provided the following explanation:

> *As described in the BLA, Eylea HD stands for High Dose of Eylea. The dose of Eylea is 2 mg and the dose of Eylea HD is 8 mg, 4 times the concentration of the currently approved product. Based on a review of the clinical trials, the safety and efficacy of Eylea and Eylea HD are the same except that the concentration in the vitreous is higher and the dosing frequency can be somewhat reduced. Clinically, there is not more than a twofold difference.*
>
> *If a different name is used, the strong similarities between Eylea and Eylea HD will be lost. Clinicians will know that it is the same molecule, just a different strength. If clinicians start to distinguish the products as Eylea 2 mg and Eylea 8 mg, there will be an assumption that Eylea 8 mg lasts 4 times as long, which is not correct. The HD term would signify a higher dose without inferring how much higher.*

Thus, at the request of DO, OPDP re-evaluated the name Eylea HD and subsequently overturned their initial objection. OPDP stated that they do not formally object to the name from a promotional perspective. DO did not provide additional comments or concerns at the initial phase of the review.

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) acknowledged the initial findings of OPDP's assessment for Eylea HD, and DMEPA 1 additionally concurred with the re-evaluation of OPDP's assessment for Eylea HD.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Eylea HD.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name.[e]

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a single word that contains a modifier "HD". Regeneron indicated in their submission that the base of the proposed proprietary name, Eylea, is an approved FDA proprietary name and that the suffix, HD, is used to denote "high dose". The modifier "HD" is added to the root name, Eylea, to indicate that the 8 mg intravitreal product contains a higher dose of aflibercept compared to the currently approved 2 mg intravitreal product, Eylea. Additionally, whereas Eylea is typically indicated for every 4-to-8-week dosing after the initial loading doses, Eylea HD is typically indicated for every 8-to-16-week dosing after the initial loading doses. The safety assessment of the modifier is discussed in Section 2.2.5.

[e] USAN stem search conducted on December 28, 2022.

2.2.3 Comments from Other Review Disciplines at Initial Review

On February 13, 2023, the Division of Ophthalmology (DO) forwarded a comment relating to Eylea HD at the initial phase of the review (see Section 2.1).

2.2.4 FDA Name Simulation Studies

Eighty-six (n=86) practitioners participated in DMEPA's prescription studies for Eylea HD. We note that one participant in the inpatient written prescription study, two participants in the Computerized Physician Order Entry study, and one participant in the outpatient written prescription study interpretated the proposed name as "Eylea" or "Eylia", omitting the modifier, "HD." We assess the risk of omitting the modifier in Section 2.2.5. Beyond these misinterpretations, the responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

2.2.5 Safety Assessment of the Modifier

The applicant currently markets the active ingredient, aflibercept, under the name Eylea (BLA 125387). The product is currently available as a 2 mg/0.05 mL strength for the treatment of patients with nAMD, DME, DR, RVO and ROP. The applicant proposes a 8 mg/0.07 mL strength of aflibercept under BLA 761355, for the treatment of patients with nAMD, DME and DR. For The applicant proposes to use the name, Eylea HD, for their proposed product. The differences between the proposed product and the currently marketed product are listed in Table 1 under Section 1.2 of our review.

1. **Evaluation of the use of the same root name, "Eylea"**
   Eylea has been marketed as the proprietary name for aflibercept since approval on November 18, 2011. We note that Eylea and Eylea HD share the same active ingredient, dosage form, and route of administration. Our routine postmarketing surveillance has not identified any signals attributed to name confusion involving Eylea. Thus, we do not object to the use of the root name, Eylea, for this product.

2. **Evaluation of the use of a modifier to differentiate the products**
   The proposed product represents a new strength of Eylea (8 mg/0.07 mL vs. 2 mg/0.05 mL). Thus, the applicant proposes to use the modifier "HD" to denote "high dose", signifying that the 8 mg injection for intravitreal use contains a higher dose than the currently approved 2 mg injection for intravitreal use. We evaluated the use of a modifier to determine if the naming strategy helps to differentiate the proposed Eylea HD product from the currently marketed Eylea product.

   It is not uncommon to use modifiers to denote a product line extension, as the addition of a modifier may signal to healthcare providers that this product differs from the currently marketed Eylea product.

   As part of our evaluation, we considered the risks should the modifier "HD" be omitted or not acknowledged on a prescription, as seen in the FDA Prescription Simulation Study. We note that omission and oversight of a modifier is cited in literature as a

common cause of medication error.[f] During the FDA Prescription Simulation study, there was one inpatient participant and two CPOE participants who misinterpreted Eylea HD as Eylea. We also consulted with the Division of Ophthalmology clinical colleagues to determine the clinical significance of patient harm (if any) if the products were to be confused for one another. For example:

- Product selection errors (i.e., if a patient is intended to receive Eylea but instead receives Eylea HD or if a patient is intended to receive Eylea HD but instead receives Eylea)
- Wrong frequency of administration errors (i.e., Eylea HD administered at intervals less than every 8 weeks instead of every 8 to 16 weeks as intended or Eylea administered at intervals greater than every 8 weeks instead of every 4 to 8 weeks as intended)
- Confusion that the strength of Eylea HD is four times higher than that of Eylea (i.e., if a patient is intended to receive Eylea 2 mg, but instead receives Eylea HD 2 mg; or if a patient is intended to receive Eylea HD 8 mg, but instead receives Eylea 8 mg)
- Administration of Eylea HD for an unapproved indication (i.e., RVO or ROP)

According to our clinical colleagues, *"the data in the trials submitted by Regeneron demonstrates essentially equal efficacy between the 2 mg and 8 mg products, with the 8 mg [product] able to last a few week longer duration."* Our clinical colleagues did not convey significant concerns regarding wrong product administration (i.e., Eylea HD administration instead of Eylea or vice versa) but stated that, *"theoretically, there could be more inflammation with every 4 week administration [of Eylea HD] than every 8 to 16 week administration [if the 8 mg product were administered every 4 weeks following initial dosing]…but the initial rates of inflammation are very low so there is room before it becomes a significant problem."* Given the data demonstrates similar efficacy, we considered that it could be expected that there may be a decrease in efficacy if Eylea 2 mg was inadvertently administered every 16 weeks instead of every 4 to 8 weeks.

Our clinical colleagues further stated "*Intraocular injections are only given by ophthalmologists. All ophthalmologists know that when you inject intraocularly, you must control the volume otherwise you will cause an increase in the intraocular pressure. 100 microliters [0.1 mL] is the most you can give to most people without causing a significant rise in intraocular pressure. An ophthalmologist is not going to try to give 0.2 mL because they know it would cause pressure problems. In the other direction, if an ophthalmologist mistakenly gives 0.05 mL of the Eylea HD, they will end up giving 5.7 mg. Considering how close the response rate is between 2 mg and 8 mg, 5.7 mg is likely to be minimally distinguishable from 8 mg.*"

Furthermore, our clinical colleagues did not convey any significant concerns regarding accidental administration of Eylea HD for RVO or ROP.

[f] Lesar TS. Prescribing errors involving medication dosage forms. J Gen Intern Med. 2002 Aug; 17(8):579-87.

We considered the notion of introducing a new proprietary name for this product and have concluded that doing so still carries the risk of medication errors, specifically, those associated with therapeutic duplication and overdose. Although the proposed naming strategy is not devoid of risk because modifiers may be omitted or overlooked, they can assist in differentiating products and may help to prevent potential selection errors when used. Thus, based on the totality of this information, we do not object to the use of a modifier for this product as it may provide an added measure of safety. Furthermore, label and labeling mitigations can help minimize the residual risk of product selection errors.

3. **Evaluation of the proposed modifier "HD"**
   We evaluated the modifier "HD" meaning "High Dose" in a previous review and concluded that "*Although 'HD' is used in different medical settings to mean a variety of things, it has not been identified as a cause for misinterpretation leading to medication errors.*"[g] Given that HD is already used to mean "high dose" in other drug names and because the proposed 8 mg strength is intended for use to obtain the higher dose of 8 mg within the Eylea product line, we find the use of the modifier "HD" acceptable as it does not pose any additional risks for misinterpretation.

In summary, we find the use of the root name, Eylea, acceptable for the proposed product. Additionally, we find that the addition of the modifier "HD" to the root name may provide an additional layer of safety in differentiating the 2 mg/0.05 mL formulation from the 8 mg/0.07 mL formulation. Although the naming strategy presents some risk of product selection error if the modifier is dropped or overlooked, we find the residual risk of medication error acceptable based on input from the clinical review team. Therefore, based on the totality of the information considered above, we do not object to the proposed name, Eylea HD, for the proposed product.

2.2.6 Communication of DMEPA's Determination

On March 27, 2023, DMEPA 1 communicated our determination to the Division of Ophthalmology (DO).

3 CONCLUSION

The proposed proprietary name, Eylea HD, is conditionally acceptable.

If you have any questions or need clarifications, please contact Oyinlola Fashina, OSE project manager, at 301-796-4446.

3.1 COMMENTS TO REGENERON PHARMACEUTICALS, INC.

We have completed our review of the proposed proprietary name, Eylea HD, and have concluded that this name is conditionally acceptable.

[g] Wilson V. Proprietary Name Review for Isentress HD (NDA 022145/S-036). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 24. OSE RCM No.: 2016-9439903.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[h]

[h] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names7F[i]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name

[i] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016.

with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.	
Orthographic Checklist	Phonetic Checklist

Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

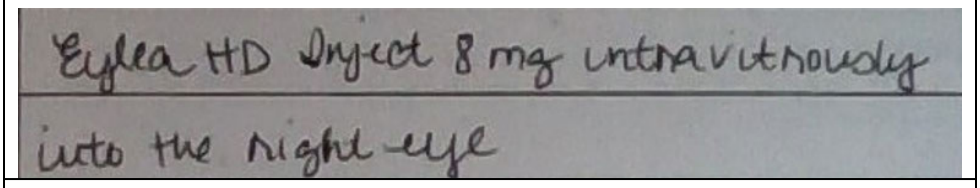
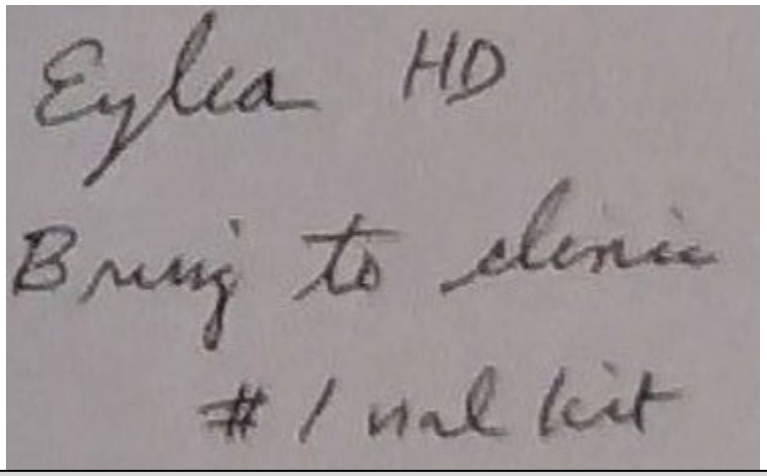
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Eylea HD Study (Conducted on January 6, 2023)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order:  Outpatient Prescription:  	Eylea HD Bring to clinic #1 vial kit
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Eylea HD	

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Eylea HD

258 People Received Study

86 People Responded

Total	**24**	**23**	**21**	**18**	
INTERPRETATION	**INPATIENT**	**CPOE**	**VOICE**	**OUTPATIENT**	**TOTAL**
AILIA HD	0	0	1	0	1
AYLEA HD	0	0	1	0	1
EILEYA HD	0	0	1	0	1
EYELIA HD	0	0	1	0	1
EYLCA HD	0	0	0	1	1
EYLEA	1	2	0	0	3
EYLEA GD	0	0	0	1	1
EYLEA HD	22	21	1	7	51
EYLEA HD INJECTION	1	0	0	0	1
EYLIA	0	0	0	1	1
EYLIA HD	0	0	0	8	8
ILEA HD	0	0	6	0	6
ILEAH HD	0	0	4	0	4
ILEEYA HD	0	0	2	0	2
ILIA HD	0	0	1	0	1
ILIEA HE	0	0	1	0	1
ILIIA HD	0	0	1	0	1
ILYA HD	0	0	1	0	1

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/s/

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