

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217171Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 217171 Assessment # 1

Drug Product Name	Pegcetacoplan ophthalmic solution for intravitreal injection
Dosage Form	Solution
Strength	150 mg/mL
Route of Administration	Intravitreal injection
Rx/OTC Dispensed	Rx
Applicant	Apellis Pharmaceuticals, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	May 26, 2022	All disciplines
Quality Amendment	Jul 8, 2022	Drug substance
Quality Amendment	Jul 21, 2022	Drug product
Quality Amendment	Aug 4, 2022	Quality microbiology
Quality Amendment	Aug 9, 2022	Manufacturing process
Quality Amendment	Aug 12, 2022	Quality microbiology
Quality Amendment	Sep 7, 2022	Drug product
Quality Amendment	Sep 21, 2022	Drug product
Quality Amendment	Sep 26, 2022	Quality microbiology
Quality Amendment	Oct 19, 2022	Quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Daniel Jansen	Zhengfu Wang
Drug Product	Elise Luong	Chunchun Zhang
Manufacturing	Sureshbabu Dadiboyena	Kamal Tiwari
Microbiology	Yarery Smith	Yeissa ChabrierRosello
Biopharmaceutics	NA	NA



QUALITY ASSESSMENT



Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Elise Luong	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	NA		(b) (4)
	III			NA		

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

Document	Application Number	Description
IND	124784	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics		Adequate on the drug product impurities limit	9/15/2022	Abel Eshete
Pharmacology/Toxicology		Adequate	10/4/2022	Erin Ruhland
CDRH		NA		The product is regulated as a drug
Clinical		Adequate on the proposed operating room setting, and bioassay limit	7/12/2022; 9/14/2022	Wiley Chambers
Other		NA		

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

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

The product is regulated as a drug because the syringes are not part of the NDA submission. (b) (4)

OPMA has issued an overall acceptable recommendation for all the facilities on Jun 27, 2022. Therefore, NDA 217171 is recommended approval from Product Quality perspective.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Pegcetacoplan ophthalmic solution, 150 mg/mL is a sterile aqueous, (b) (4) solution for intravitreal injection packaged in a single-dose (b) (4) vial 3-mL glass vial containing (b) (4) mg of pegcetacoplan in (b) (4) mL solution to deliver the single dose of 0.1mL solution.

Proposed Indication(s) including Intended Patient Population	For treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Duration of Treatment	Each dose is 0.1 mL solution containing 15 mg of pegcetacoplan
Maximum Daily Dose	15 mg/day. As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance pegcetacoplan is a synthetic peptide conjugate composed of two identical pentadecapeptides covalently bound to the

ends of a linear 40-kDa polyethylene glycol molecule. Sufficient CMC information including manufacturing process, impurities profile and stability data was provided.

Drug Product: Adequate

Pegcetacoplan ophthalmic solution for intravitreal injection, 150 mg/mL is a sterile, colorless to light yellow clear solution. All the excipients are compendial.

The revised drug product specifications are acceptable and include the following quality attributes: description, identification, assay, bioassay, related substances, viscosity, minimum fill weight, pH, particulate matter, osmolality, endotoxin bacteria and sterility. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities and (b) (4) impurities showed low risk.

Extractable/leachable studies were performed; none of the extracted substances have a level of concentration above the safety level.

Pegcetacoplan ophthalmic solution for intravitreal injection, 150 mg/mL is packaged in a clear Type (b) (4) glass vial and sealed with a (b) (4)

(b) (4) rubber stopper. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted three drug product primary stability batches at the proposed commercial scale with 12 months stability data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°C/60%RH). All the quality attributes met the specifications.

Photostability study indicated the drug product is sensitive to light and a cautious statement will be included in the labeling. Freeze-thaw study with three cycles were conducted to support the proposed shipping plan.

Therefore, the expiration date of 12 months for commercial products is granted when stored at 2 °C to 8 °C (35 °F to 46 °F).

The storage statement is (b) (4) and will be finalized at the OND's labeling meeting.

Labeling: Adequate

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

Manufacturing: Adequate

The manufacturing process includes (b) (4). All the process related concerns have been resolved. All the manufacturing

sites are acceptable based on the previous inspection history and manufacturing capability.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. (b) (4)
 Sterility and bacterial endotoxins are tested for release of finished drug product.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay (API), stability	- Formulation - Container closure - Raw materials	L	(b) (4)	L	
Impurities	- Formulation - Container closure - Process parameters - Scale/equipment	H		L	
pH	- Formulation - Container closure - Process parameters - Scale/equipment	L		L	
Viscosity	- Formulation - Container closure - Process parameters - Scale/equipment	H		L	
Particulate matter	- Formulation - Container closure	L		L	
Sterility	- Formulation - Container closure - Process parameters - Scale/equipment	H		M	

Bacteria endotoxin	• Formulation • Container closure • Process parameters - Scale/equipment	H	(b) (4)	L	

D. List of Deficiencies for Complete Response

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

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

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

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Oct 26, 2022

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CHAPTER IV: LABELING
IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	SYFOVRE	On 04/20/22, DMEPA found the proposed proprietary name is conditionally acceptable
Established name(s)	Pegcetacoplan	Adequate
Route(s) of administration	Intravitreal injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Solution, 150 mg/mL  (b) (4)	Adequate

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	The drug product is in a single-dose vial and the vial is for single use only.	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

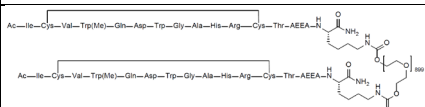
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Remove the carton from the refrigerator. Keep vial in carton at room temperature for at least 15 minutes but no longer than 8 hours. Fill the syringe immediately prior to the injection. Inspect the solution. It is a clear, colorless to light yellow aqueous solution. Do not use if: particulates, cloudiness, or discoloration are visible, the vials show signs of damage or tampering, or if the expiration date has passed. Use aseptic technique.	Adequate. There is an instruction for aseptic technique and injection procedure

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Solution	Adequate
Strength(s) in metric system	15 mg/0.1 mL, single-dose vial	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	The drug product is in a single-dose vial and the vial is for single use only.	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name	SYFOVRE	On 04/20/22, DMEPA found the proposed proprietary name is conditionally acceptable.
Established name(s)	Pegcetacoplan (APL-2)	Adequate
Dosage form(s) and route(s) of administration	Solution, intravitreal injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Tetralose dihydrate Glacial acetic acid Sodium acetate trihydrate Water for Injection Sodium hydroxide	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Trehalose dihydrate (5.95 mg) Glacial acetic acid (0.0895 mg) Sodium acetate trihydrate (0.0353 mg) Water for Injection Sodium hydroxide (for adjustment of a target pH of 5.0)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This product is sterile	Adequate

Pharmacological/ therapeutic class	Missing	CMC comment conveyed to OND
Chemical name, structural formula, molecular weight	 Molecular weight: 43.5 kDa C₁₉₇₀H₃₈₄₈N₅₀O₉₇₄S₄	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Section 3.2.S.1.2	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Solution	Adequate
Strength(s) in metric system	15 mg/0.1 mL	Adequate
Available units (e.g., bottles of 100 tablets)	(b) (4)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, colorless to light yellow aqueous solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	SYFOVRE (pegcetacoplan) intravitreal injection is supplied as a clear, colorless to light yellow solution. Each SYFOVRE carton contains one single-dose, (b) (4) glass vial (b) (4) 15 mg/0.1 mL solution.	Adequate

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Refrigerate SYFOVRE between 2 °C to 8 °C (36 °F to 46 °F). Store the vial in the original carton to protect from light. Do not shake. Do not use beyond the expiration date on the carton.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Refrigerate SYFOVRE between 2 °C to 8 °C (36 °F to 46 °F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A

Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Assessment: There is no other sections of labeling.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Apellis Pharmaceuticals, Inc. 100 Fifth Avenue Waltham MA 02451	Adequate

2.0 PATIENT LABELING

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

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

Dose vial label



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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	SYFOVRE	On 04/20/22, DMEPA found the proposed proprietary name is conditionally acceptable.
Dosage strength	15 mg/0.1 mL Single-Dose Vial	Adequate
Route of administration	Injection	Adequate
Net contents (e.g., tablet count)	15 mg/0.1 mL	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Refrigerate at 2 °C to 8 °C (36 °F to 46 °F). Protect from light.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use).	Single-Dose Vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The product does not contain alcohol.	Adequate
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Apellis Pharmaceuticals, Inc., 100 Fifth Avenue Waltham WA 01451	Adequate
Medication Guide (if applicable)	There is a statement of (b) (4) [REDACTED]	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Drug product is a novel route of administration, there is no USP.	Adequate
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling:

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND

during labeling negotiations with the applicant. CMC team has the following comments for the labeling review team:

1. Drug product labeling review of Full Prescribing Information, in Section 11 Description, also provide the Pharmacological/Therapeutic class.
2. In Section 1.14.1.1 SYVOVRE Draft Container Label and Carton Label, we have the following comments:
 - (a) Under the tradename, add the word 'Intravitreal' before the word 'injection'.
 - (b) Add (b) (4) in a single dose vial'.
 - (c) Refrigerate at 2 °C to 8 °C (36 °F to 46 °F).

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

Other than the comments listed on page 91, the product labels are acceptable from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 10/03/22
Secondary Assessor Name and Date (and Secondary Summary, as needed): ChunChun Zhang, Ph.D., 10/07/2022



Elise
Luong

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Chunchun
Zhang

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	217171
Assessment Cycle Number	01
Drug Product Name/ Strength	Pegcetacoplan/150 mg/mL
Route of Administration	intravitreal injection
Applicant Name	Apellis Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Geographic atrophy (GA) secondary to age-related macular degeneration (AMD)/DO
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)
Review Date	10/20/2022

Assessment Recommendation: Adequate

Assessment Summary: The subject drug product is a sterile solution for intravitreal administration. (b) (4)

(b) (4) Sterility and bacterial endotoxins are tested for release of finished drug product. (u) (*)

List Submissions Being Assessed (table):

Document(s) Assessed (Seq. #)	Date Received
Original submission (0001)	05/26/2022
IR amendment (0003)	07/08/2022
IR amendment (0008)	08/04/2022
IR amendment (0009)	08/09/2022
IR amendment (0010)	08/12/2022
IR amendment (0016)	09/26/2022
IR amendment (0017)	10/19/2022

Remarks: This submission has been granted priority review status.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Microbiology review D (b) (4) M18R01.docx, dated 03/15/2022 is referenced for the depyrogenation of the (b) (4)
- Microbiology review D (b) (4) M05R01.docx, dated 04/01/2022 is referenced for the sterilization and depyrogenation relevant to the (b) (4).

S DRUG SUBSTANCE

The information pertinent to the manufacturing of the drug substance (APL-2) was not included in this review (b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

• **Drug product composition –**

Ingredient	Quality Standard	Function	Quantity per mL	Quantity per vial
Pegcetacoplan (APL-2)	In-house standard	Drug Substance	150.0 mg	15.0 mg
Trehalose dihydrate	NF/Ph.Eur./JP	(b) (4)	59.5 mg	5.95 mg
Glacial acetic acid	USP/Ph.Eur./JP		0.895 mg	0.0895 mg
Sodium acetate trihydrate	USP/Ph.Eur./JP		0.353 mg	0.0353 mg
Sodium hydroxide	NF/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Glacial acetic acid	USP/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Water for Injection	USP/Ph.Eur.	Solvent	q.s. to 1.0 mL	q.s. to 0.1 mL

• **Drug product description –**

The drug product is a sterile, aqueous, (b) (4) solution for intravitreal administration. The vial is for single use only.

• **Description of container closure system –**

Configuration	Component	Description	Manufacturer
15 mg/ 0.1 mL	Vial	(b) (4)	(b) (4)
	Stopper		
	Seal		

Assessment: Adequate

The applicant has provided an adequate description of the drug product, its composition, and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Smith

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Yeissa
Chabrier Rosello

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