

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761077Orig1s000

PRODUCT QUALITY REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	May 17, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Joslyn Brunelle, PhD, Product Quality Reviewer TL OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761077
Applicant:	Amgen Inc.
Submission Date:	May 17, 2017
Product:	Aimovig (erenumab-aooe)
Dosage form(s):	injection
Strength and Container-Closure:	70 mg/mL single-dose prefilled syringe and single-dose prefilled autoinjector
Indication, dose, route, and frequency of administration:	An anti-CGRP (calcitonin gene-related peptide) receptor antibody indicated for prevention of migraine: 140 mg once monthly administered as two consecutive subcutaneous injections of 70 mg each using the single-dose prefilled autoinjector or single-dose prefilled syringe
Background and Summary Description:	The Applicant submitted BLA 761077 for Aimovig (erenumab-aooe) on May 17, 2017 for the prophylaxis of migraine in adults.
Recommendations:	The container labels (submitted December 1, 2017), carton labeling (submitted May 11, 2018), prescribing information (submitted May 16, 2018), and patient information labeling and instructions for use (submitted May 17, 2018) for Aimovig (erenumab-aooe) injection, 70 mg/mL single-dose prefilled syringe and single-dose prefilled autoinjector for subcutaneous administration are acceptable from a quality perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels for compliance to the applicable requirements in the Code of Federal Regulations and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, patient information labeling, instructions for use, container labels, and carton labeling for Aimovig (erenumab-aooe) injection, 70 mg/mL single-dose prefilled syringe and single-dose prefilled autoinjector were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100, and USP standards.

The container labels (submitted December 1, 2017), carton labeling (submitted May 11, 2018), prescribing information (submitted May 16, 2018), and patient information labeling and instructions for use (submitted May 17, 2018) for Aimovig (erenumab-aooe) injection, 70 mg/mL single-dose prefilled syringe and single-dose prefilled autoinjector are acceptable (see Appendix D) from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted May 17, 2017

<\\cdsesub1\evsprod\bla761077\0001\m1\us\annotated-draft-labeling-text.pdf>)

Instructions for Use (submitted May 17, 2017 <\\cdsesub1\evsprod\bla761077\0001\m1\us\pfs-70mg-instructions-for-use.pdf>, <\\cdsesub1\evsprod\bla761077\0001\m1\us\pfs-140-mg-instructions-for-use.pdf>, <\\cdsesub1\evsprod\bla761077\0001\m1\us\autoinjector-70mg-instructions-for-use.pdf>, and <\\cdsesub1\evsprod\bla761077\0001\m1\us\autoinjector-140mg-instructions-for-use.pdf>)

Patient Information (submitted March 30, 2018

<\\cdsesub1\evsprod\bla761077\0057\m1\us\draft-ppi.pdf>)

Appendix B: Other (N/A)

Appendix C: Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
<u>Proper Name</u> (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: <i>considered a partial label (see below)</i>	☐ No ☐ Yes ☒ N/A
<u>Manufacturer name, address, and license number</u> (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: <i>considered a partial label (see below)</i>	☐ No ☐ Yes ☒ N/A
<u>Lot number or other lot identification</u> (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) Comment/Recommendation: <i>considered a partial label (see below)</i>	☐ No ☐ Yes ☒ N/A
<u>Expiration date</u> (21 CFR 610.60, 21 CFR 201.17) Comment/Recommendation: <i>considered a partial label (see below)</i>	☐ No ☐ Yes ☒ N/A
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60 Comment/Recommendation: <i>single-dose PFS and autoinjector</i>	☐ No ☐ Yes ☒ N/A
<u>Statement: "Rx only"</u> 21 CFR 610.60 21 CFR 201.100 Comment/Recommendation: Consider relocating "Rx Only" to appear in the upper right corner of the prefilled autoinjector container label to allow for prominence of other critical information on the principal display panel such as dosage form and discard statement. <i>The applicant revised as requested.</i>	☐ No ☒ Yes ☐ N/A
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A

¹ Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

<u>No Package for container</u> 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
<u>Partial label</u> 21 CFR 610.60 21 CFR 201.10 Comment/Recommendation: Remove the term (b) (4) and replace it with the proper name "erenumab". <i>The applicant revised as requested.</i> Add the dosage form "injection" to appear underneath the proper name in the identical font size and color as the proper name. You may accommodate this change by removing the licensed manufacturer address (Thousand Oaks, CA 91320) and listing only the licensed manufacturer name and U.S. license number as follows: "Amgen Inc. U.S. License No. 1080". We consider this to be a partial label and the licensed manufacturer address is not required information on partial labels. Revise the order of appearance of the licensed manufacturer name so that the U.S. License No. 1080 appears after the licensed manufacturer name. <i>The applicant revised as requested.</i>	☒ No ☐ Yes ☐ N/A
<u>No container label</u> 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
<u>Ferrule and cap overseal</u> Comment/Recommendation: None (PFS/Autoinjector)	☐ No ☐ Yes ☒ N/A
<u>Visual inspection</u> 21 CFR 610.60 Comment/Recommendation: None (PFS/Autoinjector)	☐ No ☐ Yes ☒ N/A
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Preparation instructions</u> 21 CFR 201.5 Comment/Recommendation: <i>See recommendation to add discard unused portion statement below.</i>	☒ No ☐ Yes ☐ N/A
<u>Package type term</u> 21 CFR 201.5	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials/PFS may be needed to obtain a single dose. Revise the term "(b) (4)" to read "single-dose" and include a statement of "Discard unused portion" as follows:

"Single-dose. Discard unused portion". To accommodate this important information, you may consider removing the container closure statement from the container label ("prefilled syringe" or "autoinjector") since we consider this to be a partial label and the container closure statement is not required information on partial labels.

The applicant revised as requested.

<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
<u>Strength</u> 21 CFR 201.10 21CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☐ No ☒ Yes ☐ N/A

<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100 Comment/Recommendation: None considered partial label thus must appear on the carton, PI, and IFU (if applicable).	☐ No ☒ Yes ☐ N/A
<u>Inactive ingredients</u> 21 CFR 201.100 Comment/Recommendation: None considered partial label thus must appear on the carton, PI, and IFU (if applicable).	☐ No ☒ Yes ☐ N/A
<u>Storage requirements</u> Comment/Recommendation: The storage information is not required for a partial label. Consider removing to reduce clutter or revise the storage statement from (b) (4) to read: "Store at 2°C to 8°C (36°F to 46 °F)" per USP definitions (see USP chapter <659> Packaging and Storage Requirements). <i>The applicant revised as requested.</i>	☐ No ☒ Yes ☐ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label⁵ Evaluation

<u>Regulations, Guidance and CDER Best Labeling Practices</u>	<u>Conforms</u>
<u>Proper name</u> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10) Comment/Recommendation: Remove the term (b) (4) and replace it with the proper name "erenumab". Add the dosage form "injection" to appear underneath the proper name in the identical font size and color as the proper name. <i>The applicant revised as requested.</i>	☒ No ☐ Yes ☐ N/A
<u>Manufacturer name, address, and license number</u> 21CFR 610.61 Comment/Recommendation: To comply with 21 CFR 610.61(b), ensure that the U.S. license number appears after the licensed manufacturer name and address as follows: "Manufactured by Amgen Inc. Address US License No. 1080" <i>The applicant revised as requested.</i>	☒ No ☐ Yes ☐ N/A

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

<u>Lot number or other lot identification</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
<u>Preservative</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: To reduce clutter and redundancy, remove the statement "Sterile, preservative-free solution" from the principal display panel. This information is already in the quantitative and qualitative ingredient list on the side panel. <i>The applicant revised as requested.</i>	
<u>Number of containers</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the strength statement in the colored circles to the appropriate strength presentation for this dosage form: "70 mg/mL". Per USP General Chapters <7> Labeling, strength per single mL should be expressed as mg/mL. For cartons that contain two autoinjectors or two prefilled syringes, revise the strength statement in the colored circles from (b) (4) to read "70 mg/mL". <u>Applicant Response:</u> For the two-count cartons, the applicant revised to read: 70 mg/mL (in blue circle) + 70 mg/mL (in blue circle) (b) (4) (in purple circle). <u>FDA response:</u> Revise (b) (4) (in purple circle) to read "140 mg/2 mL" to reflect the appropriate strength presentation for this dosage form. <u>Applicant Response:</u> For the PFS and autoinjector 2-count cartons, the applicant revised as requested. Acceptable. <u>Applicant Response:</u> For the one-count cartons, the Applicant added a colored circle (b) (4) presentation. <u>FDA response:</u> We previously informed the applicant that the appropriate strength presentation for this dosage form is "70 mg/mL". Per USP General Chapters <7> Labeling, strength per single mL should be expressed as mg/mL. (b) (4) <u>Applicant Response:</u> For the one-count cartons, the applicant revised as requested. Acceptable.	
<u>Storage temperature</u>	☒ No

21 CFR 610.61	☐ Yes ☐ N/A
Comment/Recommendation: For consistency with the prescribing information, provide complete storage information for the end user, and space for documentation of date removed from the refrigeration. Add the storage statement "Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If needed, patients/caregivers may store Aimovig at room temperature up to 25°C (77°F) for up to (b) (4) days. Once stored at room temperature, do not place back in the refrigerator. Discard after (b) (4) days. Write the date removed from the refrigerator ____/____/____." <i>The applicant revised as requested.</i> Revise the storage statement on the principal display panel to read "Store at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do Not Freeze. Do Not Shake. Discard Any Unused Portion." <i>The applicant revised as requested.</i> <i>Ensure that the optional room temperature storage period is revised to 7 days based on your drug product stability specifications on all carton labeling</i> <i>The applicant revised as requested</i>	
Handling: "Shake Well", "Do not Freeze" or equivalent (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61 Comment/Recommendation: single-dose	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21CFR 610.61	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: <i>"This Product Contains Dry Natural Rubber." Appears in carton.</i>	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Revise the package type term in the qualitative and quantitative ingredient list to "single-dose" and the proper name from (b) (4) to "erenumab". <i>The applicant revised as requested.</i>	

<u>Source of the product</u> 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
<u>Minimum potency of product</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100 Comment/Recommendation: Unbold the Rx only statement as it competes with other important information and relocate the Rx only statement to the upper portion of principal display panel near the NDC number. <i>The applicant revised as requested.</i>	☐ No ☒ Yes ☐ N/A
<u>Divided manufacturing</u> 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
<u>Distributor</u> 21 CFR 610.64	☐ No ☐ Yes ☒ N/A
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
<u>Preparation instructions</u> 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
<u>Package type term</u> 21 CFR 201.5 Comment/Recommendation: Revise the term (b) (4) to read "single-dose" throughout carton labeling. <i>The applicant revised as requested.</i>	☒ No ☐ Yes ☐ N/A
<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
<u>Spanish-language (Drugs)</u>	☐ No

21 CFR 201.16	☐ Yes ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A

Prescribing Information and Patient Labeling Evaluation

<u>Regulations</u>	<u>Conforms</u>
<u>PRESCRIBING INFORMATION</u>	
<u>Highlights of prescribing information</u>	
<u>PRODUCT TITLE</u> 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
<u>DOSAGE AND ADMINISTRATION</u> 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
<u>DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
<u>Comment/Recommendation:</u> Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL", not "mg/1 mL". Revise the strength presentation from "70 mg/1 mL" to read "70 mg/mL" <i>The Applicant revised as requested</i>	

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☐ No ☒ Yes ☐ N/A
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the strength presentation from "70 mg/1 mL" to read "70 mg/mL" per USP General Chapters <7> Labeling. Ensure identifying characteristics are consistent throughout the PI. clear to opalescent, colorless to light yellow solution <i>The Applicant revised as requested</i>	
6.2 IMMUNOGENICITY Draft Guidance for Industry: Labeling for Biosimilar Products	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We relocated and revised the language for this standard statement based on our current labeling best practice. <i>The Applicant revised as requested</i>	
11 DESCRIPTION (21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We deleted (b) (4) this paragraph discusses the drug substance. <i>The Applicant revised as requested</i> We added dosage form to second paragraph per 21 CFR 201.57(c)(12). <i>The Applicant revised as requested</i> Per OND best labeling practices list all inactive ingredients in alphabetical order (see USP Chapter <1091>) followed by their quantitative information that is deliverable in 1 mL using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection. Ensure that the list of inactive ingredients and their quantitative information provided here and on the carton labeling are consistent. <i>The Applicant revised as requested</i>	
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added the dosage from per 21 CFR 201.57(c)(17) <i>The Applicant revised as requested</i> Ensure identifying characteristics are consistent throughout the PI. <i>The Applicant revised as requested</i> Revised the optional temperature storage period to seven days based on your drug product stability specifications <i>The Applicant revised as requested</i>	
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64	☒ No ☐ Yes

Comment/Recommendation: Revise (b) (4) to read "Marketed by: Name and address of company number 1 and Name and address of company number 2" <i>The Applicant revised as requested</i>		☐ N/A
INSTRUCTIONS FOR USE and PATIENT INFORMATION		
<u>TITLE (NAMES AND DOSAGE FORM)</u>		☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added the dosage form <i>The Applicant revised as requested</i> We revised to the appropriate package type term and to be consistent with the PI <i>The Applicant revised as requested</i>		
<u>STORAGE AND HANDLING</u>		☐ No ☒ Yes ☐ N/A
<u>INGREDIENTS</u>		☐ No ☐ Yes ☒ N/A
<u>MANUFACTURER INFORMATION</u> 21 CFR 610.61, 21 CFR 610.64		☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Add the U.S. license number to appear following the licensed manufacturer name and address per 21 CFR 610.61(b) as follows: Manufactured by: Applicant on Form FDA 356h Address US License No. xxxx <i>The Applicant revised as requested</i> Revise (b) (4) to read "Marketed by: Name and address of company number 1 and Name and address of company number 2" <i>The Applicant revised as requested</i>		

APPENDIX D. Acceptable Labels and Labeling

The following were submitted via email and the enclosed agreed-upon labeling text are acceptable from a product quality perspective:

- Prescribing Information (submitted May 17, 2018- see below)
- Instructions for Use (submitted May 16, 2018- see below)
- Patient Information (submitted May 16, 2018- see below)

Container Labels (submitted December 1, 2017)

Clarify the difference between the (b) (4) container label and the white container label provided in the submission.

Amaen Response:

(b) (4)

Autoinjector

Visual Representation

(b) (4)

Prefilled syringe

Visual Representation

(b) (4)



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 5/17/2018 03:39:10PM
GUID: 50814c7000007a3d59329f660d8ddf02



Joslyn
Brunelle

Digitally signed by Joslyn Brunelle
Date: 5/17/2018 03:43:57PM
GUID: 508da6da000265eafdde3cc7507da20b

First Approval for Indication

Recommendation:
BLA Approval

BLA 761077
Review Number: 1
February 16, 2018

Drug Name/Dosage Form	AIMOVIG/Erenumab-aooe, injection
Strength/Potency	70 mg/mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	Migraine
Applicant/Sponsor	Amgen

Product Overview

Erenumab is a human monoclonal antibody of the immunoglobulin IgG2 subclass which is manufactured in mammalian (CHO) cells. Erenumab specifically binds to the extracellular domain of the calcitonin gene-related peptide receptor (CGRP-R) and prevents interaction with the neuropeptide CGRP. This is the first BLA approval for a CGRP receptor antagonist for the treatment of migraine headaches in adults. Two doses (70mg and 140mg) were evaluated during clinical studies. Erenumab Drug product is a single-use, sterile, preservative-free, colorless to light yellow solution; supplied as 70 mg/mL for monthly subcutaneous (SC) injection via prefilled syringe (PFS) or autoinjector (AI/pen). Note that two PFS/AI are needed to administer the 140mg dose.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Xuhong Li	OBP/DBRR-IV
Drug Product	Xuhong Li	OBP/DBRR-IV
Immunogenicity	Xuhong Li	OBP/DBRR-IV
Labeling	Vicky Borders-Hemphill	OBP
Facility	Laura Fontan/Peter Qiu	OPF/DIA
Microbiology DS	Kathleen Jones/ Reyes Candau-Chacon	OPF/DMA
Microbiology DP	Lakshmi Narasimhan/Patricia Hughes	OPF/DMA
Application Team Lead	Joslyn Brunelle	OBP/DBRR-IV
Regulatory Business Process Manager	Oumou Barry	OPRO

Mutidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Lana Chen	OND/ODE1/DNP
Cross-disciplinary Team Lead	Heather Fitter	OND/ODE1/DNP
Medical Officer	Laura Jawidzik	OND/ODE1/DNP
Pharm/Tox	Edmund Nesti/Lois Freed	OND/ODE1/DNP
Clinical Pharmacology	Girish Bende/Sreedharan Sabarinath	OTS/OCF/DCP1
Statistics	Jinnan Liu/Kun Jin	OTS/OB/DB1

a. Names:

- i. Proprietary Name: Aimovig
- ii. Trade Name: Aimovig
- iii. Non-Proprietary/USAN: Erenumab-aooe
- iv. CAS name: 1582205-90-0
- v. Common name: AMG 334
- vi. INN Name: N/A
- vii. Compendial Name: N/A
- viii. OBP systematic name: MAB HUMAN (IGG2) ANTI Q16602 (CALRL_HUMAN) [AMG334]

b. Pharmacologic category: CGRP-receptor antagonist

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0003 - Stability update	June 16, 2017
0005 - IR #1	June 27, 2017
0008 - IR #2	June 29, 2017
0013 - IR #3	July 13, 2017
0026 - IR #4	October 27, 2017
0038 - IR #5	December 18, 2017
0039 - Stability update (IR #5)	January 5, 2018
0041 - IR #6	January 8, 2018
0043 - IR #7	January 12, 2018
0048 - IR #8	January 26, 2018
0047 - IR #9	January 30, 2018
0050 - IR#10	February 14, 2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
(b) (4)	Type III	(b) (4)	(b) (4)	3	N/A	
	Type III			1	Adequate	
	Other			3	N/A	
	Other			3	N/A	
	Other			3	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows:
2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.)

B. Other documents: None

3. Consults:

DISCIPLINE/ TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH/ODE	May 2017	Complete	Approval	Robert Meyer & John McMichael
CDRH/OC	May 2017	Complete	Approval	Daniel Ramsey

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761077 for Erenumab-aooe manufactured by Amgen. The data submitted in this application is adequate to support the conclusion that the manufacture of Erenumab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

C. Draft Approval Action Letter Language:

- Manufacturing location:
 - Drug Substance: Amgen Thousand Oaks (ATO), Thousand Oaks, California
 - Drug Product: Amgen Manufacturing Limited (AML), Juncos, Puerto Rico
- Fill size and dosage form
 - Prefilled Syringe: 70mg/1 mL
 - Autoinjector: 70mg/1 mL
- Dating period:
 - Drug Product: 24 months: 2-8 °C
 - Drug Substance: (b) (4)
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
- Exempt from lot release
 - Yes; Rationale, for exemption - specified product (exempt according to 21 CFR 601.2a)

D. Benefit/Risk Considerations:

Erenumab-aooe is a human IgG2 monoclonal antibody that binds to calcitonin gene-related peptide receptor (CGRP-R) which is proposed to treat migraines in adults. While approved therapies exist to treat migraines, there are many patients that have failed existing treatments. There is unmet medical need for new treatments for migraine that are efficacious, convenient, and allow long term sustained benefits in the patient population.

Amgen's integrated control strategy

(b) (4)

Amgen product quality attribute assessment has identified critical quality attributes based on their potential to impact patient safety and product efficacy. Overall, Amgen's control strategy is sufficient to ensure product quality. The drug substance and drug product manufacturing processes are well controlled and can reproducibly produce pure and potent product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The drug product manufacturing process provides sterility assurance. The analytical methods for release and stability testing are validated for specificity, precision, repeatability, linearity, accuracy, and robustness. The manufacturing facilities for drug substance (Amgen Thousand Oaks, ATO, California) and drug product (Amgen Manufacturing Limited, AML, Puerto Rico) are recommended for approval. (b) (4)

[REDACTED]

[REDACTED]

Overall product quality, immunogenicity assay, and labeling (reviewed by OBP), microbiology (reviewed by DMA), facilities (reviewed by DIA), and device (reviewed by CDRH) are located as separate documents in Panorama.

The assay used to detect anti-erenumab antibodies are suitable for use in clinical studies. Overall, clinical studies indicate that anti-drug antibody (ADA) levels are low. There are limitations for the neutralizing assay due to poor drug tolerance; however, Amgen has data from the safety follow up (when drug exposures are low) to indicate that patients are negative for neutralizing antibodies.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy
Cell based bioassay (<i>potency</i>)	Directly linked to efficacy	Intrinsic to molecule	(b) (4)
High molecular weight species (Aggregates) <i>Product related impurities</i>	Efficacy, Immunogenicity	Introduced during manufacturing process and storage	
Charge variants <i>Product related impurities</i>	Efficacy	Introduced during manufacturing process and storage	
Fragments <i>Product related impurities</i>	Efficacy, PK	Introduced during manufacturing process and storage	
Disulfide isoforms <i>Product related impurities</i>	Efficacy; (b) (4) [REDACTED] [REDACTED]	Introduced during manufacturing process and storage	
Deamidation/Isomerization <i>Product related impurities</i>	Efficacy	Introduced during manufacturing process and storage	

(b) (4)

Glycosylation <i>Product related impurities</i>	Impacts half-life (PK)	Introduced during manufacturing process	
--	---------------------------	---	--

B. Drug Substance erenumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (Type)	Risk	Origin	Control Strategy
Bioburden <i>(contaminant)</i>	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	(b) (4)
Endotoxin <i>(contaminant)</i>	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process	
Protein concentration <i>(general)</i>	Efficacy	Manufacturing process/formulation	
(b) (4) <i>(general)</i>	Stability, efficacy	Formulation	
pH <i>(general)</i>	Stability, efficacy	Formulation	

Osmolality (<i>general</i>)	Stability, safety	Formulation	(b) (4)
Appearance and color (<i>general</i>)	Safety	Manufacturing process and Formulation	
Host Cell Proteins (<i>process related impurity</i>)	Safety and immunogenicity	During manufacturing process	
Host Cell DNA (<i>process related impurity</i>)	Safety	During manufacturing process	
(b) (4) (<i>process related impurity</i>)	Safety and immunogenicity	(b) (4)	
Adventitious Viruses and Mycoplasma (<i>process related impurity</i>)	Safety	Contamination during manufacture	
(b) (4)	Safety	(b) (4)	
(<i>process related impurity</i>)			

a) Description:

Erenumab is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass. Each heavy chain contains 456 amino acids with 4 intrachain disulfide bonds. Each light chain contains 216 amino acids with 2 intrachain disulfide bonds. Erenumab contains 6 interchain disulfide bonds for a total of 18 intrachain and interchain disulfide bonds. The CH2 domain of the heavy chain contains one N-linked glycan on Asparagine (Asn) 306, with the predominant species identified as asialylated core fucosylated bi antennary structures with varying degrees of terminal galactosylation. The theoretical mass is 148,761 Daltons and the experimentally determined mass is 148,767 Daltons.

b) Mechanism of Action (MoA):

Binds to calcitonin gene-related peptide type 1 receptor (CGRP-R) and inhibits CGRP ligand induced signaling. CGRP is a neuropeptide expressed in and released by sensory nerves and acts as a potent vasodilator upon binding to its receptor (CGRP-R). CGRP-R is a G-protein coupled receptor that has been shown to produce cyclic adenosine monophosphate (cAMP) as part of its signal transduction mechanism. CGRP has been implicated in migraines and its levels are elevated in the blood during a migraine attack.

c) Potency Assay:

The AMG 334 cell-based potency assay uses a stable Chinese hamster ovary (b) (4) (CHO-(b) (4)) cell line expressing human CGRP-R. The addition of the CGRP neuropeptide results in the production of intracellular cAMP via signaling from the CGRP-R. When erenumab is added, there is a dose-dependent decrease in the amount of cAMP produced by the cells.

The amount of cAMP generated is measured using competitive homogeneous LANCE® time-resolved fluorescence energy transfer (TR-FRET) technology. A fluorescence signal is generated when cAMP labelled with Alexa Fluor® 647 dye and an anti-cAMP monoclonal antibody-cryptate are brought within close proximity by binding. Due to the competition between native cAMP produced by the cells and the labeled cAMP for binding to the cryptate-labeled anti-cAMP monoclonal antibody, the signal generated is inversely proportional to the concentration of cAMP produced by the cells. Test sample potency is determined by comparing the test sample response to the AMG 334 reference standard and is reported as relative potency.

Erenumab does not induce Fc effector function (ADCC or CDC).

d) Reference Materials:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

e) Critical starting materials or intermediates:

(b) (4)

f) Manufacturing process summary:

(b) (4)



g) **Container closure:**



h) **Dating period and storage conditions:**

Drug substance can be stored  (b) (4)



C. Drug Product AIMOVIG Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy
Sterility (<i>contaminant</i>)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)
Endotoxin (<i>contaminant</i>)	Safety, purity, and potential immunogenic reactions	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	
Container closure integrity (<i>sterility assurance</i>)	Safety Failure in closure integrity may lead to contamination (loss of sterility) of DP or evaporation/leakage	Might be impacted by storage	

	(impacting concentration or content)		
Protein concentration (<i>general</i>)	Efficacy	Formulation	(b) (4)
Appearance, Color, Clarity (<i>general</i>)	Safety	Formulation	
Polysorbate 80 (<i>general</i>)	Stability, efficacy	Formulation	
Subvisible particles (<i>product and/or process related impurities</i>)	Immunogenicity, safety	Manufacturing process and container closure system	
Leachables/extractables (<i>process related impurities</i>)	Safety	Manufacturing equipment and container closure system	
pH (<i>general</i>)	Safety	Formulation	
Osmolality (<i>general</i>)	Safety	Formulation	
Deliverable volume (<i>general</i>)	Efficacy/Dosing	Manufacturing process	
Breakboose and Extrusion Force (<i>general, device</i>)	Safety	Device performance	
Injection time (<i>general, device</i>)	General	Device performance	
Identity (ELISA)	Safety, Efficacy	Intrinsic to molecule	

(general)			
-----------	--	--	--

a) Potency and Strength:

Erenumab is supplied as 70mg/mL solution in a single dose prefilled syringe (PFS) or autoinjector (AI). Both PFS and AI contain 1.0 mL deliverable volume.

b) Summary of Product Design:

Erenumab is a sterile, single use, preservative free solution for subcutaneous injection that can be self-administered, given by caregiver (b) (4)

(b) (4) Erenumab is liquid, practically free from particles, colorless to light yellow solution.

c) List of Excipients:

(b) (4) acetate, 7.3% (w/v) sucrose, 0.010% (w/v) polysorbate 80, pH 5.2

d) Reference Materials:

same reference material used for Drug Substance and Drug Product

e) Manufacturing process summary:

(b) (4)

f) Container closure:

(b) (4) Type 1 glass prefilled syringe (PFS) with a staked needle covered with an elastomeric needle shield and a (b) (4) plunger-stopper (b) (4) with a (b) (4). The elastomeric needle shield is made from natural rubber, protects the needle cannula, and is supplemented with an outer plastic rigid cover (rigid needle shield).

SureClick autoinjection/pen (AI/Pen) consists of a PFS contained within two subassemblies. The front subassembly hold the PFS with staked needle and non-rigid needle shield. The rear subassembly contains a plunger rod (b) (4) that drives dose delivery.

The sponsor conducted a Leachable study and data at 14 and 27 months indicates that limits are below the level of toxicological concern.

g) **Dating period and storage conditions:**

24 months at 2-8°C

The data included in the BLA support storage for up to 7 days at 25°C once removed from refrigerator, as described in the labeling.

h) List of co-package components, if applicable: none

D. Novel Approaches/Precedents: none

E. Any Special Product Quality Labeling Recommendations:

Store at 2-8°C. Protect from light. Do not freeze or shake. If removed from refrigeration, should be kept at (b) (4) room temperature (25°C) and must be used within 7 days.

F. Establishment Information:

OVERALL RECOMMENDATION: APPROVAL					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug substance MANUFACTURER Drug Substance In-process, release, and stability testing Master and working cell bank production and storage	AMGEN INC 1 AMGEN CENTER DR THOUSAND OAKS, CA US 91320 1730	2026154	Acceptable	Sept 2017 PAI inspection-NA I No FDA 483 observations	Acceptable
Drug Substance RELEASE and STABILITY TESTING	AMGEN MANUFACTURING LIMITED PO BOX 4060 CARR 31 KM 24.6 JUNCOS, PR 00777	1000110364	Acceptable	N/A	Acceptable
Drug Substance RELEASE and STABILITY TESTING	AMGEN TECHNOLOGY IRELAND POTTERY ROAD LAOGHAIRE, IRELAND	3002808497	Acceptable	N/A	Acceptable

(b) (4)			Acceptable	N/A	Acceptable
			Acceptable	N/A	Acceptable
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug Product MANUFACTURER Drug Product In-process, RELEASE and STABILITY TESTING PACKAGING and LABELING Autoinjector assembly Distribution	AMGEN MANUFACTURING LIMITED (AML) PO BOX 4060 RD 31 KM 24.6 JUNCOS, PR 00777	1000110364	Acceptable	N/A Hurricane assessments completed by Div II, Last EI and profile SVS acceptable	Acceptable
Drug Product RELEASE and STABILITY TESTING	AMGEN TECHNOLOGY IRELAND POTTERY ROAD LAOGHAIRE, IRELAND	3002808497	Acceptable	N/A	Acceptable
Drug Product release and stability testing Device manufacturer	AMGEN INC 1 AMGEN CENTER DR THOUSAND OAKS, CA US 91320 1730	2026154	Acceptable	N/A	Acceptable
Container closure integrity testing	(b) (4)		Acceptable	N/A	Acceptable

G. Facilities:

The inspection of drug substance manufacturing site (ATO, California) was conducted on September 27-29 and October 2-3, 2017 by CDER/OPQ/OPF/DMA and OPQ/OBP and was classified as NAI.

The inspection of drug product manufacturing site (AML, Puerto Rico) was waived; it is acceptable based on inspection and compliance history.

For additional information see the Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management:

a. Drug Substance:

Protocols approved:

- [REDACTED] (b) (4)
- Qualification of future Working Cell Bank protocol
- Qualification of future Reference Standard protocol
- [REDACTED] (b) (4)
- [REDACTED]
- Post-approval stability protocol

b. Drug Product

Protocols approved:

- Post-approval stability protocol

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/source material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non-Primate Mammalian Cell Substrate/source material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity	X		
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]			X
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)	X		
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]			X
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	X	
23.		Process	X	
24.		Analytical Methods	X	
25.		Other	X	
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)	X – DP only		
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients	X	
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin	X	
35.		Novel	X	
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other {fill-in}			X



Joel
Welch

Digitally signed by Joel Welch
Date: 2/28/2018 08:12:15AM
GUID: 508da6dc0002673d83d264d81364d6cf



Joslyn
Brunelle

Digitally signed by Joslyn Brunelle
Date: 2/27/2018 05:01:30PM
GUID: 508da6da000265eafdde3cc7507da20b



Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 2/28/2018 10:06:35AM
GUID: 508da717000297bcbfce0919f8c09594



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 2/28/2018 09:40:14AM
GUID: 508da7480002bfb5825e149b2b4eb91d

BLA 761077

Product (Erenumab)

Amgen

Xuhong Li, Ph.D., Quality Reviewer
Joslyn Brunelle, Ph.D., Team Lead

Division of Biotechnology Review & Research IV (DBRRIV)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: 761-077
2. Review Date: December 08, 2017
3. Primary Review Team:
 - a. **Medical Officer:** Laura Jawidzik, Heather Fitter (CDTL)
 - b. **Pharm/Tox:** Edmund Nesti
 - c. **Product Quality Team:** Xuhong Li (DS, DP and immunogenicity) (OPQ/OBP)
Kathleen Jones (DS) and Lakshmi Narasimhan (DP) (OPQ/OPF/DMA)
 - d. **Facilities:** Laura Fontan (OPQ/OPF/DIA)
 - e. **Clinical Pharmacology:** Girish Bende
 - g. **OBP Labeling:** Vicky Borders-Hemphill (OPQ/OBP)
 - h. **RBPM:** Oumou Barry (OPQ/OPRO), Lana Chen (OND/DNP)
4. Major GRMP Deadlines:
 - a. Filing Meeting: June 29, 2017; filing 74D letter sent July 20, 2017
 - b. Mid-cycle meeting: October 17, 2017
 - c. Wrap-up meeting: March 22, 2018
 - d. Primary review due: February, 2018
 - e. PDUFA action date: May 17, 2018

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Filing review memo	
Mid Cycle Communication	11/01/2017
Information Request #1	12/01/2017
Information Request #2	12/20/2017
Information Request # 3	01/19/2018
Information Request # 4	01/25/2018

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761077/0001	05/17/2017	yes
STN 761077/0003	06/16/2017	yes
STN 761077/0038	12/18/2017	yes
STN 761077/0039	01/05/2018	yes
STN 761077/0043	01/12/2018	yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Aimovig
- b. Trade Name: Aimovig
- c. Non-Proprietary Name/USAN: Erenumab
- d. CAS Name: 1582205-90-0

e. Common Name: anti-human CGRP-R (calcitonin gene-related peptide type 1 receptor) monoclonal antibody

f. INN Name: Erenumab

h. OBP systematic name: MAB HUMAN (IGG2) ANTI Q16602 (CALRL_HUMAN) [AMG334]

i. Other names: AMG 334 (company code)

8. Pharmacological Category:

9. Dosage Form: liquid in a single-dose pre-filled syringe
liquid in a single-dose Pre-filled autoinjector (AI/Pen)

10. Strength/Potency:

(i): The concentration/strength of the Drug Product: 70mg/mL

(ii): Type of potency assay(s): Cell-based bioassay using CHO (b) (4) cell line expressing CGRP-R. Amgen uses fluorescence energy transfer (FRET) based technology to measure the amount of intracellular cAMP signaling from the CGRP-R.

11. Route of Administration: Subcutaneous

12. Referenced Drug Master Files (DMF):

DMF/MAF #	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	
			Yes	
			Yes	
			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
				No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	Reviewed by CDRH

13. Inspectional Activities:

The pre-license inspection of the drug substance manufacturing site at Amgen thousand oak facility (1 Amgen Center Drive, Thousand Oaks, CA 91320) was conducted from Sep 27, 2017 to Oct 3, 2017 by Xuhong Li and Joslyn Brunelle from OPQ/OBP, Scott Nichols and Kathleen Jones from OPQ/OPF/DMA. The inspection was system based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. No Form FDA483 was issued. It was recommended that the inspection be classified as no action indicated.

14. Consults Requested by OBP:

The device reviews for the PFS and the Autoinjector (AI/Pen) were done by Robert Meyer/John McMichael and Daniel Ramsey/Matthew Krueger (CDRH); review memos will be uploaded in Panorama.

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: none

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Aimovig™ (erenumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been adequately validated, and multiple production batches demonstrated consistent production process and product quality. The proposed shelf life (b) (4) and 24 months at 5°C (with up to 7 days storage at (b) (4) room temperature) for the drug product is supported by the stability data. It is recommended that Aimovig™ (erenumab) be approved for human use and under conditions specified in the package insert.

II. List of Deficiencies to be Communicated

None

III. List of Post-Marketing Commitments/Requirements

None

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Amgen claims a categorical exclusion for erenumab pursuant to 21 CFR §25.15(d) under the provisions of 21 CFR §25.31(c) and FDA (1998) guidance for industry. Erenumab is considered “naturally occurring in the environment” and when exposed to the environment is not expected to significantly alter the concentration of the substance, its metabolites, or degradation products in the environment.

Reviewers comment: *Categorical Exclusion is appropriate for this product and is granted.*

V. Primary Container Labeling Review

The OBP carton and container technical assessment was reviewed by Vicky Borders-Hemphill and will be uploaded as a separate file in Panorama.

VI. Review of Common Technical Document-Quality Module 3.2 and module 2.3

The review of Module 2.3 and 3.2 are included in this review.

VII. Review of Immunogenicity Assays- Module 5.3.1.4: include at the end of this review.

TABLE OF CONTENTS

S Drug Substance	10
3.2.S.1. General Information.....	10
3.2.S.1.2 Nomenclature	10
3.2.S.1.2 Structure	10
3.2.S.1.3 General Properties	12
3.2.S.2 Manufacture	13
3.2.S.2.1 Manufacturer(s)	13
3.2.S.2.2 Description of Manufacturing Process and Process Controls	14
3.2.S.2.2.1 Batch and Scale Definition	14
3.2.S.2.2.2 Cell Culture and Harvest	14
3.2.S.2.2.3 Purification	18
3.2.S.2.2.4 Filling, Storage, and Transportation	23
3.2.S.2.3 Control of Materials	24
3.2.S.2.3.1 Control of Source and Starting Materials Not of Biological Origin	24
3.2.S.2.3.2 Control of Source and Starting Materials of Biological Origin	25
3.2.S.2.3.3 Source, History, and Generation of the Cell Substrate	25
3.2.S.2.3.4 Cell Banking System, Characterization, and testing	26
3.2.S.2.4 Controls of Critical Steps and Intermediates	31
3.2.S.2.5 Process Validation and/or Evaluation.....	36
Process validation	36
1. (b) (4)	36
2.	40
3.	43
4.	44
5.	46
Transportation Qualification	48
3.2.S.2.6 Manufacturing Process Development	48
Process Characterization	48
1. Cell Culture and Harvest	49
2. Purification	53
3. (b) (4)	64
Integrated control Strategy.....	65

Product Comparability	71
S.2.S.3 Characterization.....	84
3.2.S.3.1 Elucidation of Structure and Other Characteristics	85
1. Biochemical Characterization.....	85
2. Biophysical Characterization	90
3. Biological Characterization.....	90
4. Forced Degradation.....	92
3.2.S.3.2 Impurities	93
1. Product Related Impurities	93
2. Process Related Impurities.....	94
3.2.S.4 Control of Drug Substance	97
3.2.S.4.1 and 3.2.S.4.5 Specification and Justification of Specification	97
3.2.S.4.4 Batch Analyses	100
3.2.S.4.2 and 3.2.S.4.3 Analytical Method, Validation and Transfer	100
3.2.S.5 Reference Standards or Materials	121
Qualification of Primary Reference Standard	122
Primary Reference Standard Stability	125
Protocol – Qualification of Future Reference Standards	127
3.2.S.6 Container Closure System	129
3.2.S.7 Stability	131
3.2.S.7.1 Stability Summary and Conclusions.....	131
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment	132
3.2.S.7.3 Stability Data	134
P Drug Product.....	138
3.2.P.1 Description and Composition of the Drug Product	138
3.2.P.2 Pharmaceutical Development	139
3.2.P.2.1 Components of the Drug Product	139
3.2.P.2.1.1 Drug Substance	139
3.2.P.2.1.2 Excipients	139
3.2.P.2.2 Drug Product.....	140
3.2.P.2.2.1 Formulation Development	140
3.2.P.2.2.2 Overages	144
3.2.P.2.2.3 Physicochemical and Biological Properties.....	144
3.2.P.2.3 Manufacturing Process Development.....	144

Process Development	144
Process Characterization	150
3.2.P.2.4 Container Closure System	162
Extractable and Leachable	163
3.2.P.2.5 Compatibility	165
Prefilled Syringe	165
AI/Pen	169
3.2.P.3 Manufacture	170
3.2.P.3.1 Manufacturer(s)	170
3.2.P.3.2 Batch Formula	171
3.2.P.3.3 Description of Manufacturing Process and Process Controls	172
3.2.P.3.4 Control of Critical Steps and Intermediates	174
3.2.P.3.5 Process Validation and/or Evaluation	174
Formulation and Filling Process Validation	174
Transportation Qualification	180
3.2.P.4 Control of Excipients	182
3.2.P.5 Control of Drug Product	183
3.2.P.5.1 & 5.6 Specifications & Justifications	183
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	188
Deliverable volume	188
Breakloose and Extrusion	188
Injection time for AI/Pen	190
3.2.P.5.4 Batch Analyses	190
3.2.P.5.5 Characterization of Impurities	190
3.2.P.6 Reference Standards or Materials	191
3.2.P.7 Container/Closure System	191
3.2.P.8 Stability	193
3.2.P.8.1 Stability Summary and Conclusion	193
3.2.P.8.2 Post-Approval Stability Commitment	196
3.2.P.8.3 Stability Data	197
3.2.A.2 Adventitious Agents Safety Evaluation (see ICH Q5A)	201
Qualification of small scale models	202
(b) (4) small scale model and qualification results:	202
Viral Clearance Studies	206

3.2.A.3 Novel Excipients	211
3.2.R Regional Information	211
3.2.R.1 Executed Batch Records.....	211
3.2.R.2 Method Validation Package	211
3.2.R.3 Comparability Protocols for DS Manufacturing Site Change.....	211
Proposed Process Changes.....	212
Risk Assessment, Development/Characterization Studies and Process Validation.....	213
Comparability.....	213
Appendix: Immunogenicity Assay Review	218
Anti-AMG 334 Binding Antibodies Assay.....	218
Method Description and Other General Information.....	218
Method Validation (Screening Assay and Confirmatory Assay)	220
Neutralizing Antibody Assay.....	227

Note: The reviewer's notes and comments are provided in italics throughout the text. The pictures, graphs, and tables in this review are directly taken from the IND submission unless otherwise specified.

S Drug Substance

3.2.S.1. General Information

3.2.S.1.2 Nomenclature

Recommended International Non-proprietary Name (INN):

erenumab

Chemical name(s):

anti-human CGRP-R (calcitonin gene-related peptide type 1 receptor) monoclonal antibody

Chemical abstracts service(CAS) #:

1582205-90-0

Amgen laboratory code name:

AMG 334

United States Adopted Name (USAN):

erenumab

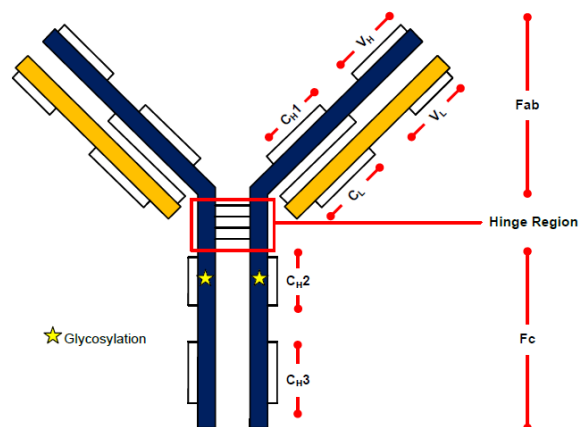
3.2.S.1.2 Structure

AMG 334 is a human monoclonal antibody of the immunoglobulin G2 (IgG2) contains a total of 36 cysteine residues that forms intra-chain and inter-chain disulfide bonds among the 2 heavy chains and 2 λ light chains.

The theoretical amino acid sequence was verified by peptide mapping with LC-MS/MS. The molecular formula for the predominant AMG 334 heavy chain isoform is C₂₂₃₄H₃₄₃₁N₅₉₅O₆₈₀S₂₀ (C-terminal Gly⁴⁵⁵, N-terminal pyroglutamic acid, not including N-linked glycans). The molecular formula for the predominant AMG 334 light chain isoform (N-terminal pyroglutamic acid) is C₁₀₀₂H₁₅₆₅N₂₆₉O₃₂₇S₅. The theoretical mass of fully assembled AMG 334 antibody is 145,870 Da without N-linked glycans, or 148,761 Da with 2 A2G0F glycans (1 per heavy chain). The experimentally determined predominant AMG 334 mass is 148,767 Da.

The schematic diagram of the structure and theoretical amino acid sequence of AMG 334 are copied from the submission and presented below:

Figure 1. Schematic of AMG 334 Structure



Heavy chains are shown in blue and light chains are shown in orange
Disulfide linkages are indicated by solid black lines
V_H is the variable domain of the heavy chain
C_{H1}, C_{H2}, and C_{H3} are the constant domains of the heavy chain
V_L is the variable domain of the light chain
C_L is the constant domain of the light chain

Figure 2. Encoded Primary Amino Acid Sequence of AMG 334 Heavy Chain

1	Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	Ser	Leu	Arg
	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	R	S	L	R
20	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Phe	Gly	Met	His	Trp	Val	Arg
	L	S	C	A	A	S	G	F	T	F	S	S	F	G	M	H	W	V	R
39	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Val	Ile	Ser	Phe	Asp	Gly	Ser	Ile
	Q	A	P	G	K	G	L	E	W	V	A	V	I	S	F	D	G	S	I
58	Lys	Tyr	Ser	Val	Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys
	K	Y	S	V	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K
77	Asn	Thr	Leu	Phe	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
	N	T	L	F	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y
96	Cys	Ala	Arg	Asp	Arg	Leu	Asn	Tyr	Tyr	Asp	Ser	Ser	Gly	Tyr	Tyr	His	Tyr	Lys	Tyr
	C	A	R	D	R	L	N	Y	Y	D	S	S	G	Y	Y	H	Y	K	Y
115	Tyr	Gly	Met	Ala	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr
	Y	G	M	A	V	W	G	Q	G	T	T	V	T	V	S	S	A	S	T
134	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
	K	G	P	S	V	F	P	L	A	P	C	S	R	S	T	S	E	S	T
153	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
	A	A	L	G	C	L	V	K	D	Y	F	P	E	P	V	T	V	S	W
172	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser
	N	S	G	A	L	T	S	G	V	H	T	F	P	A	V	L	Q	S	S
191	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln
	G	L	Y	S	L	S	S	V	V	T	V	P	S	S	N	F	G	T	Q
210	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Thr	Val
	T	Y	T	C	N	V	D	H	K	P	S	N	T	K	V	D	K	T	V
229	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro
	E	R	K	C	C	V	E	C	P	P	C	P	A	P	P	V	A	G	P
248	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
	S	V	F	L	F	P	P	K	P	K	D	T	L	M	I	S	R	T	P
267	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn
	E	V	T	C	V	V	V	D	V	S	H	E	D	P	E	V	Q	F	N
286	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
	W	Y	V	D	G	V	E	V	H	N	A	K	T	K	P	R	E	E	Q
305	Phe	Asn*	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu
	F	N	S	T	F	R	V	V	S	V	L	T	V	V	H	Q	D	W	L
324	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu
	N	G	K	E	Y	K	C	K	V	S	N	K	G	L	P	A	P	I	E
343	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
	K	T	I	S	K	T	K	G	Q	P	R	E	P	Q	V	Y	T	L	P
362	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
	P	S	R	E	E	M	T	K	N	Q	V	S	L	T	C	L	V	K	G
381	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
	F	Y	P	S	D	I	A	V	E	W	E	S	N	G	Q	P	E	N	N
400	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
	Y	K	T	T	P	P	M	L	D	S	D	G	S	F	F	L	Y	S	K
419	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
	L	T	V	D	K	R	R	W	Q	Q	G	N	V	F	S	C	S	V	M
438	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys**
	H	E	A	L	H	N	H	Y	T	Q	K	S	L	S	L	S	P	G	K

* Asn³⁰⁶ is a consensus glycosylation site

(b) (4)

Figure 3. Encoded Primary Amino Acid Sequence of AMG 334 Light Chain

1	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Ala	Ala	Pro	Gly	Gln	Lys	Val	Thr
	Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T
20	Ile	Ser	Cys	Ser	Gly	Ser	Ser	Ser	Asn	Ile	Gly	Asn	Asn	Tyr	Val	Ser	Trp	Tyr	Gln
	I	S	C	S	G	S	S	S	N	I	G	N	N	Y	V	S	W	Y	Q
39	Gln	Leu	Pro	Gly	Thr	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Asp	Asn	Asn	Lys	Arg	Pro	Ser
	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	N	K	R	P	S
58	Gly	Ile	Pro	Asp	Arg	Phe	Ser	G	Ser	Lys	Ser	Gly	Thr	Ser	Thr	Thr	Leu	Gly	Ile
	G	I	P	D	R	F	S	G	S	K	S	G	T	S	T	T	L	G	I
77	Thr	Leu	Gln	Thr	Gly	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gly	Thr	Trp	Asp	Ser	Arg	
	T	G	L	Q	T	G	D	E	A	D	Y	Y	C	G	T	W	D	S	R
96	Leu	Ser	Ala	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys
	L	S	A	V	V	F	G	G	G	T	K	L	T	V	L	G	Q	P	K
115	Ala	Asn	Pro	Thr	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	Ala	Asn	Lys
	A	N	P	T	V	T	L	F	P	P	S	S	E	E	L	Q	A	N	K
134	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	Ala	Val	Thr	Val	Ala	Trp
	A	T	L	V	C	L	I	S	D	F	Y	P	G	A	V	T	V	A	W
153	Lys	Ala	Asp	Gly	Ser	Pro	Val	Lys	Ala	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln
	K	A	D	G	S	P	V	K	A	G	V	E	T	T	K	P	S	K	Q
172	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys
	S	N	N	K	Y	A	A	S	S	Y	L	S	L	T	P	E	Q	W	K
191	Ser	His	Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr
	S	H	R	S	Y	S	C	Q	V	T	H	E	G	S	T	V	E	K	T
210	Val	Ala	Pro	Thr	Glu	Cys	Ser												
	V	A	P	T	E	C	S												

3.2.S.1.3 General Properties

AMG 334 is a recombinant human IgG2 monoclonal antibody produced in Chinese hamster ovary (CHO) cells. The physical chemical properties of AMG 334 are summarized in the table below:

Table 1. Physical and Chemical Properties of AMG 334

Immunoglobulin subclass	IgG2
Sequence	Human sequence
Biological Target	Specific binding to calcitonin gene-related peptide receptor (CGRP-R)
Molecular Mass ^a	145,881 Da for deglycosylated molecule 148,767 Da including glycosylation
Cysteines	36
Number of intra and inter disulfide bonds	12 intrachain and 6 interchain (18 total)
Glycosylation	N-linked site: Asn ³⁰⁶ on each heavy chain
Extinction coefficient	Theoretical: 1.5 mg ⁻¹ cm ⁻¹ mL at 280 nm Determined: 1.5 mg ⁻¹ cm ⁻¹ mL at 280 nm
Isoelectric point (pI)	Theoretical: 8.8 ^b Determined: 9.0
T _m (melting temperature) ^c	73.8°C ^d

^a Experimentally determined molecular mass

^b Theoretical isoelectric point with C-terminal glycine on both heavy chains

^c Experimentally determined melting temperature.

^d Single transition observed. Thermal transitions of the C_H2 or C_H3 domains not resolved from the Fab domain.

The mechanism of action of AMG 334 in migraine prevention is through binding to the Calcitonin gene-related peptide (CGRP) receptor, thereby blocking the action of the CGRP ligand for a prolonged period of time. The CGRP receptor is located at sites that are relevant to migraine pathophysiology (radiolabelled CGRP, mRNA expression, and immunohistochemistry studies of the rat, monkey, and human brain demonstrated expression of CGRP and its receptor in various regions of the brain including striatum, colliculi, periaqueductal gray, parabrachial nucleus, trigeminal nucleus, nucleus solitarius, cerebellum, hippocampus, and amygdala). AMG 334 exhibits a dose-dependent inhibition of CGRP signaling in in-vitro assays, which confirms its potency in blocking this pathway. The proposed cell based potency assay (for release and stability) measures the dose-dependent decrease in cAMP production caused by the binding of AMG 334 to the CGRP receptor and the subsequent inhibition of the binding of the ligand CGRP, which directly reflects the mechanism of action of AMG 334.

Reviewer's Comment: AMG 334 was engineered as an IgG2 isotype which is expected to have minimal immune effector functions and do not effectively elicit complement-dependent cytotoxicity in the presence of human complement. However, CGRP receptor is a membrane bound protein, which increases the chance of ADCC and CDC effector functions. The applicant has evaluated AMG 334 Fc functionality during biological characterization exercise and found that, while AMG 334 binds to FcγRIIa, there was no evidence of either ADCC or CDC activity. It was also found that AMG 334 binds to FcRn in a dose dependent manner. More details are presented in 3.2.S.3 below.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Drug Substance Facility Responsibilities			
Manufacturer or Testing Facility	Address	FDA Registration Numbers	Responsibility
Amgen Inc. (Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320, USA	FEI: 2026154 DUNS:039976196	Drug substance manufacture Drug substance in-process, lot release, and stability testing (b) (4) Master cell bank and working cell bank storage Working cell bank production
Amgen Manufacturing Limited (AML)	Carr. 31 KM 24.6 Juncos, Puerto Rico 00777, USA	FEI: 1000110364 DUNS: 785800020	Drug substance in-process, lot release, and stability testing
Amgen Technologies Ireland UC (Referred to as Amgen Dun Laoghaire or ADL)	Pottery Road, Dun Laoghaire, Ireland	FEI: 3002808497 DUNS: 896293920	Drug substance in-process, lot release, and stability testing

(b) (4)

124 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

P Drug Product

3.2.P.1 Description and Composition of the Drug Product

The drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection in a prefilled syringe (PFS), or a prefilled SureClick® autoinjector/pen (AI/Pen), that intends to deliver 1.0 mL of 70 mg/mL AMG 334 in (b) (4) acetate, 7.3% (w/v) sucrose, 0.010% (w/v) polysorbate 80, pH 5.2.

The primary container for the PFS presentation is a Type I glass syringe with a staked needle covered with an elastomeric needle shield and (b) (4) plunger-stopper (b) (4). The elastomeric needle shield is made from natural rubber, protects the needle cannula, and is supplemented with an outer plastic rigid cover (rigid needle shield or RNS). A plastic plunger rod is threaded into the plunger-stopper.

The AI/Pen is a single-use, disposable, handheld, mechanical (b) (4) delivery device that is provided ready-to-use, pre-assembled with a PFS. The PFS contained within the AI/Pen has a non-rigid needle shield (nRNS, a needle shield without an outer plastic rigid cover) and does not include a plastic plunger rod.

The compositions of the drug product are the same in the PFS and AI/Pen presentations, which are summarized as follows:

**Table 1. Quantitative and Qualitative Composition of 1.0 mL of 70 mg/mL
AMG 334 Drug Product per Prefilled Syringe**

Component	Reference to Standard	Function	Concentration	Quantity (per dose)
AMG 334	In house ^a	Active ingredient (b) (4)	70 mg/mL	70 mg
Sucrose	NF, PhEur, JP		7.3% (w/v)	73 mg
Polysorbate 80	NF, PhEur, JP		0.010% (w/v)	0.10 mg
(b) (4)	USP, PhEur, JP		(b) (4)	(b) (4)
	NF, PhEur, JP			
	USP, PhEur, JP			
(b) (4)				

^a Tested to internal specifications (3.2.S.4.1, Specification).

Reviewer's Comment: The drug product is intended for patient self-administration of 140 mg AMG334 once monthly as two consecutive subcutaneous injections of 70 mg each. Both PFS and AI/Pen are validated to deliver 1.0 mL of AMG334 at 70 mg/mL without excessive volume left after administration. The proposed PFS or AI/Pen presentation appears to fit the purpose of the intended use.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)



Xuhong
Li

Digitally signed by Xuhong Li
Date: 2/28/2018 11:31:45AM
GUID: 508da7210002a00c7693bc9ce497840f



Joslyn
Brunelle

Digitally signed by Joslyn Brunelle
Date: 2/28/2018 11:32:52AM
GUID: 508da6da000265eafdde3cc7507da20b



Joel
Welch

Digitally signed by Joel Welch
Date: 2/28/2018 01:25:47PM
GUID: 508da6dc0002673d83d264d81364d6cf

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 17 January 2018
To: Administrative File, **STN 761077/0**
From: Kathleen R. Jones, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV
Through: Reyes Candau-Chacon, Ph.D. Actg Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV
Subject: New 351 (a) Biologic License Application (BLA)
Applicant: Amgen Inc.
US License: 1080
Product: AMG 334, Erenumab
Dosage: 70 mg/mL Prefilled Syringe, Prefilled SureClick® AI/Pen
Indication: For prophylaxis of migraines
Facilities: Amgen Inc (Amgen Thousand Oaks/ATO)
One Amgen Center Drive
Thousand Oaks, CA 91320
FEI: 2026154
Receipt Date: 17 May 2017
Action date: 17 May 2018

Recommendation for Approvability: BLA 761077/0 as amended is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Amgen Inc. has submitted 351(a) BLA 761077 to obtain approval of AMG 334. AMG 334 is a human immunoglobulin G2 monoclonal antibody against the calcitonin gene-related peptide receptor. BLA 761077 was submitted in eCTD format on 17 May 2017. This review contains the assessment of the microbial quality attributes of AMG 334 (b) (4) drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Lakshmi Narasimhan.

Drug Substance Microbiology Information Reviewed

eCTD Sequence	Date	Description
0001	17 May 2017	Original BLA

0005	27 June 2017	IR Response; Modifications to 1.11
0043	12 Jan 2018	IR Response, Modifications to 3.2.S.2.1, 3.2.S.2.2, 3.2.S.2.4, 3.2.R, 3.3
0047	30 Jan 2018	IR Response, Modifications to 3.2.S.2.2, 3.2.S.2.4

Full FDA Information Requests are provided at the end of this review memo.

Product Quality Microbiology Assessment: Drug Substance
MODULE 3.2.S DRUG SUBSTANCE

S.1 General Information

AMG 334 is a human IgG2 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells. AMG 334 is proposed to bind to human calcitonin gene-related peptide receptor in a dose dependent manner, thereby neutralizing its effects.

The description is satisfactory

S.2 Manufacture

S.2.1 Manufacture(s)

Manufacturing, release testing, and stability testing facilities for AMG 334 drug substance can be found below. The information in the table below is from Table 1 and Table 2 in section 3.2.S.2.1 from the submission.

Site	Responsibility
Amgen Inc. (Amgen Thousand Oaks/ATO) One Amgen Center Drive, Thousand Oaks, CA USA FEI: 2026154	Drug substance manufacture Drug substance in-process, lot release, and stability testing (b) (4) MCB and WCB storage WCB production
Amgen Manufacturing Limited (AML) Carr. 31 KM 24.6 Juncos, Puerto Rico 00777 USA FEI: 1000110364	Drug substance in-process, lot release, and stability testing
Amgen Technologies Ireland UC (Amgen Dun Laoghaire/ADL) Pottery Road Dun Laoghaire Ireland FEI: 3002808497	Drug substance in-process, lot release, and stability testing

(b) (4)

(b) (4)

*Contract Testing Laboratory

Reviewer's comment: The following information request was sent to clarify microbial testing facilities.

Section 3.2.S.2.1 Manufacture(s)

- 1.) Indicate testing sites for bioburden and bacterial endotoxin in-process and release tests.
Update section 3.2.S.2.1 of the BLA accordingly.

Applicant's Response: In Amendment 0043 dated 12 January 2018 the applicant stated that all in-process and release testing for bioburden and bacterial endotoxin was being performed at ATO. Additionally, drug substance endotoxin release testing can be performed at ADL. No microbial testing is performed at AML. See 3.2.S.4.3 for validation of endotoxin testing at ADL.

The description is satisfactory

S.2.2 Overview of Manufacturing Process

(b) (4)

Satisfactory

Conclusions

- I. This BLA as amended was reviewed from a product quality microbiology perspective, and it is recommended for approval.
- II. Information and data in this submission not related to microbial control of the drug substance is noted and should be reviewed by the appropriate division.
- III. A pre-license inspection was conducted at Amgen, Inc. at Thousand Oaks, CA on 27-29 September and 02-03 October 2017 by OPF/DMA (Scott Nichols and Kathleen R. Jones) and OBP (Joslyn Brunelle and Xuhong Li). No FDA Form 483 was issued. See Panorama for the current compliance status of the facilities.

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



Kathleen
Jones

Digitally signed by Kathleen Jones

Date: 2/16/2018 05:54:37AM

GUID: 5894f1f1003e8c4eacbe116ee0769c47



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon

Date: 2/16/2018 12:08:49PM

GUID: 508da7160002977f7ca389c8f849b707



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: February 02, 2018
To: Administrative File, BLA 761077
From: Lakshmi Rani Narasimhan, Ph.D., Reviewer, CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: # 1080
Applicant: Amgen Inc.
Facility: Amgen Manufacturing Ltd (AML), Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 USA (FEI # 1000110364) - Pre-filled syringe (PFS) and Autoinjector (AI)/Pen
Product: AMG 334, Erenumab
Presentation: Prefilled Syringe, Prefilled SureClick® AI/Pen (70mg/mL) for subcutaneous injection
Indications: Prophylaxis of Migraine
Due Date: May 16, 2018

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY:

Amgen Inc. submitted an application for BLA 761077 to license AMG 334 for prophylaxis of migraine in adults. Drug substance is manufactured by Amgen Inc., Thousand Oaks, CA (ATO), and drug product in pre-filled syringe (PFS) and the autoinjector (AI)/Pen are manufactured at Amgen Manufacturing Ltd. Juncos, Puerto Rico (AML).

The application submitted in eCTD format included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 Module 3, appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), and a regional section (3.2.R).

Letter of authorization (LOA) for [REDACTED] (b) (4)

INTRODUCTION

AMG 334 proposed for the prophylaxis of migraine in adults is presented in PFS and AI/Pen (70mg/mL) for subcutaneous injection.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective. For the review of drug substance aspects of the application, please see Panorama.

ASSESSMENTS**Drug Product Quality Microbiology Information Reviewed**

Sequence number	Date	Description
0001	May 17, 2017	Original
0005	June 27, 2017	IR response
0008	June 29, 2017	IR response
0026	October 27, 2017	IR response
0041	January 08, 2018	IR response

3.2.P. DRUG PRODUCT**AMG 334**

The AMG 334 drug product (DP) is supplied in two presentations, prefilled syringe (PFS) and pre-assembled autoinjector (AI). DP filling in PFS and AI assembly is performed at AML.

3.2.P.1 Description and Composition of the Drug Product (70 mg/mL PFS or AI)

Sterile, preservative-free solution of DP is supplied in a single use PFS or AI for subcutaneous injection. DP in both presentations has identical formulation and provide fixed dose of 1.0 mL of 70 mg/mL. The quantitative and qualitative composition of the DP provided in Table 1 is duplicated below:

Table 1. Quantitative and Qualitative Composition of 1.0 mL of 70 mg/mL AMG 334 Drug Product per Prefilled Syringe

Component	Reference to Standard	Function	Concentration	Quantity (per dose)
AMG 334	In house ^a	Active ingredient	70 mg/mL	70 mg
Sucrose	NF, PhEur, JP	(b) (4)	7.3% (w/v)	73 mg
Polysorbate 80	NF, PhEur, JP	(b) (4)	0.010% (w/v)	0.10 mg
(b) (4)	USP, PhEur, JP	(b) (4)	(b) (4)	(b) (4)
(b) (4)	NF, PhEur, JP	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP, PhEur, JP	(b) (4)	(b) (4)	(b) (4)

^a Tested to internal specifications (3.2.S.4.1, Specification).

Autoinjector (AI)

AI is a single-use, disposable, (b) (4) delivery device containing PFS. The PFS within the AI has a non-rigid needle shield (nRNS, a needle shield without an outer rigid cover) and does not include a plastic plunger rod.

Satisfactory

3.2.P.2 Pharmaceutical Development

(b) (4)



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 2/02/2018 12:23:49PM
GUID: 508da7160002976791592556d218b997



Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 2/02/2018 01:20:25PM
GUID: 508da717000297bcbf0919f8c09594



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 01/30/2018
To: Administrative File, STN 761077/0
From: Laura Fontan, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 1080
Applicant: Amgen, Inc.
Drug Substance: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 (FEI: 2026154)
Drug Product: Amgen Manufacturing Limited, State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 (FEI: 1000110364)
Product: Erenumab, AMG334
Dosage: 70 mg/mL, Prefilled syringe, Prefilled SureClick®AI/Pen
Indication: Treatment of prophylaxis of Migraine
Due Date: 05/17/2018

RECOMMENDATION: The compliance status of drug substance site, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 (FEI: 2026154) is acceptable based on the inspection for this product in September 2017. The compliance status of drug product site, Amgen Manufacturing Limited, State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 (FEI: 1000110364) is also acceptable based on inspection and compliance history. Final recommendation from a facility perspective for the proposed manufacturing and testing sites is to approve BLA 761077 for the drug substance manufacturing at Amgen Inc. (FEI: 2026154) and drug product manufacturing at Amgen Manufacturing Limited (FEI: 1000110364).

SUMMARY

The subject BLA proposes manufacture of Erenumab, AMG334DS and DP at the following facilities. The drug substance is manufactured at Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 (FEI: 2026154). The drug product is filled into Prefilled syringe, Prefilled SureClick®AI/Pen at 70mg/ml at Amgen Manufacturing Limited, State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 (FEI: 1000110364). A complete list of facilities associated with AMG334 manufacturing is provided in Summary tables 1 and 2. Erenumab, AMG334 DP is provided in one strength, 70 mg/mL.

The sites proposed for AMG334 DS manufacture, and testing are presented below.

Summary Table 1: Proposed Sites for AMG334, Erenumab, AMG334 DS Manufacture and Testing Operations (DS and DP) .

Facility/address	FEI	Responsibilities	Inspection History/profile
AMGEN INC 1 AMGEN CENTER DR THOUSAND OAKS, CA US 91320 1730	2026154	STORER: RELEASE TESTER: MANUFACTURER: AMG334-DS STABILITY AND RELEASE TESTER: AMG334-DP Device Manufacturer	CBI 5/8/2017-VAI 4/19/2017-NAI 3/17/2017-NAI 9/1/2016-NAI 6/6/2017 (PAI)-VAI 3/14/2016-NAI 3/12/2016-NAI PAI Sept. 2017-NAI
(b) (4)			
AMGEN TECHNOLOGY IRELAND POTTERY ROAD, DUN LAOGHAIRE, IRELAND	3002808497	RELEASE, STABILITY and IN PROCESS TESTER: AMG334-DS and DP	CTL 09/22/2017-VAI 12/08/2015-VAI 4/02/2015-VAI 3/22/2013-VAI

Reviewer Comment: *The facilities for manufacture of Erenumab, AMG334 DS are adequately described.*

—Satisfactory—

Prior Inspection History for DS Manufacturing and Testing Sites:

DRUG PRODUCT FACILITIES

3.2.P.3.1. DP Manufacturers.

The sites proposed for AMG334 DP manufacture, testing, packaging, and labeling are presented below in Summary table 2. Additionally, some DP testing operations are performed by facilities listed in Summary Table 1.

Summary Table 2. Proposed Sites for AMG334 DP Manufacture and Testing Operations

Facility/address	FEI	Responsibilities	Profile/Inspection history
AMGEN MANUFACTURING LIMITED PO BOX 4060 RD 31 KM 24.6 JUNCOS, PR 00777	1000110364	MANUFACTURER AMG334-DP STABILITY TESTER: RELEASE TESTER: AMG334-DS and DP Device Manufacturer PACKAGER: LABELER: AMG334-DP	SVS 5/10/2017-VAI 1/23/2015-VAI 8/15/2013-VAI 3/29/2012-NAI

Prior Inspection History for DP Manufacturing and Testing Sites

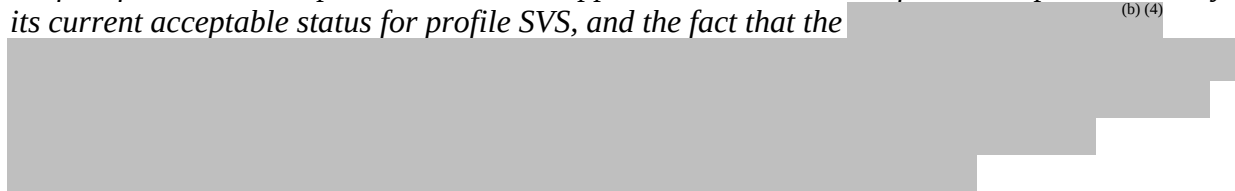
Amgen Manufacturing Limited (FEI 1000110364) AMG334 DP Manufacturing and IPC and Release Testing Site

-  (b) (4)
-  (b) (4)
-  (b) (4)

(b) (4)



Reviewer Comment: *The inspection of Amgen Manufacturing Limited for DP manufacture was waived for STN 761077/0. Based upon file review, the District recommends approval of the firm for its listed responsibilities in the application. Based on the firm's compliance history, its current acceptable status for profile SVS, and the fact that the*



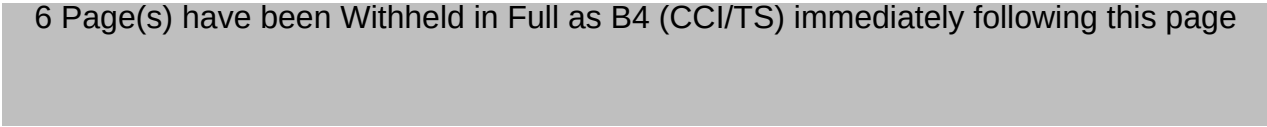
(b) (4)

—Satisfactory—

(b) (4)



6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



—*Satisfactory*—

CONCLUSION

Adequate descriptions were provided for the following sites proposed for AMG334 DS and DP manufacture:

Amgen Inc., Thousand Oaks, CA FEI: 2026154

Amgen Manufacturing Limited, Juncos, PR FEI: 1000110364

Final recommendation for the proposed manufacturing and testing sites is to approve BLA 761077/0.

Laura Fontan
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1



Laura
Fontan

Digitally signed by Laura Fontan
Date: 1/30/2018 12:28:01PM
GUID: 5408c7c5000a7d9711578ba65af66ae3



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 1/30/2018 12:39:09PM
GUID: 508da7480002bfb5825e149b2b4eb91d