CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761062Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING REVIEW

Date of review:	March 28, 2019
Reviewer:	Scott Dallas, RPh Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Chen Sun, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761062 RESUB 54
Applicant:	Amgen Inc.
Submission Date:	July 9, 2018 (resubmission); January 15, February 14, March 15 and March 20, 2019
Product:	EVENITY (Romosozumab-aqqg)
Dosage form(s):	Injection
Strength and Container-Closure:	105 mg/1.17 mL single-use prefilled syringe
Indication, dose, route, and frequency of administration:	Indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm.
Background and Summary Description:	The Applicant submitted a resubmission on July 9, 2018 in response to the Complete Response Letter dated July 13, 2017. The Applicant submitted the original BLA on July 19, 2016.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations.

A February 6, 2017 meeting occurred with representatives from DMEPA, DBRUP, OBP (quality and labeling reviewers) to discuss the package type term. It was decided to maintain the

package type term "single-use" due to concerns of confusion with using "single-dose" when 2 co-packaged prefilled syringes (PFS) are required to achieve the intended dose. All agree to relocate the package type term away from instructions on the principal display panel (PDP) that instructs healthcare providers to use 2 PFS to achieve the recommended dose.

The prescribing information submitted on March 15, 2019, medication guide submitted on March 20, 2019, container labels submitted on January 14, 2019, and carton labeling submitted on February 14, 2019 were found acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on July 9, 2018)
  \\cdsesub1\evsprod\bla761062\0001\m1\us\draft-labeling-text-uspi.doc

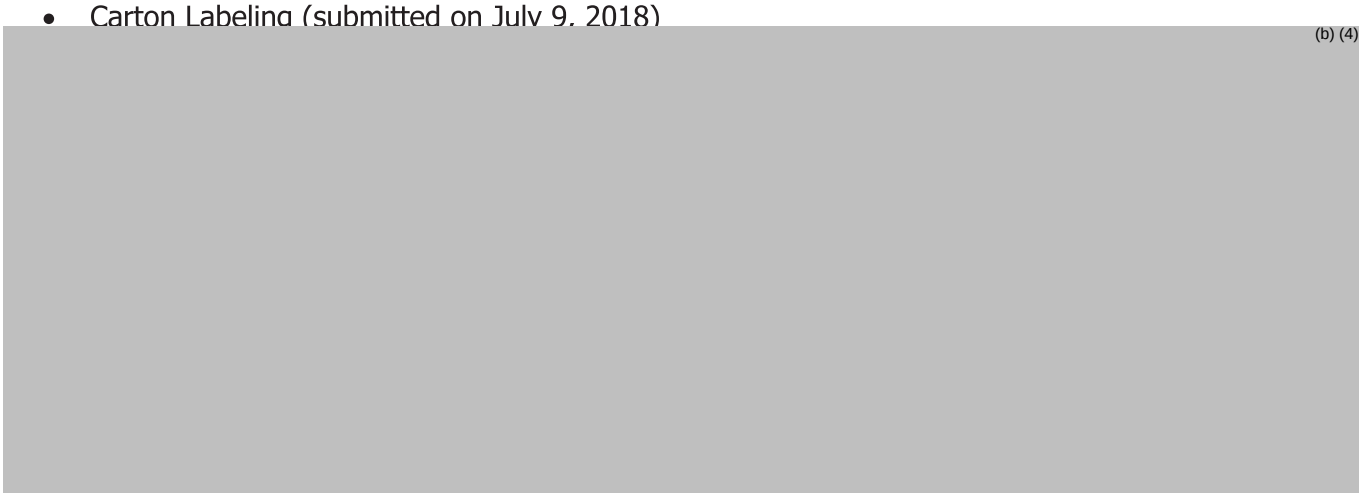
- Medication Guide (submitted on July 9, 2018)
  \\cdsesub1\evsprod\bla761062\0054\m1\us\annotated-draft-med-guide.docx

- Container Labels (submitted on April 21, 2017)

(b) (4)

- Carton Labeling (submitted on July 9, 2018)

(b) (4)



Appendix B: **Evaluation Tables**

Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label*	✓ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* *Partial label*	☐ Yes ☐ No ☒ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100)	✓ Yes ☐ No ☐ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17)	✓ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 **Comment/Recommendation:**	☐ Yes ☐ No ☒ N/A
No Package for container 21 CFR 610.60	☐ Yes ☐ No ☒ 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.

Comment/Recommendation:	
Partial label 21 CFR 610.60 21 CFR 201.10	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
No container label 21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Ferrule and cap overseal	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
Visual inspection 21 CFR 610.60	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is sufficient area on the prefilled syringe to allow for visual inspection when the label is affixed to the prefilled syringe and indicate where the visual area of inspection is located per 21 CFR 610.60(e). January 14, 2019: The Applicant provided an image of the prefilled syringe and label, which shows a clear area along the length of the syringe barrel that allows visual inspection of the contents. The applicant's response is acceptable.	
NDC numbers 21 CFR 201.2 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
Route of administration 21 CFR 201.5 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Preparation instructions 21 CFR 201.5	☐ Yes ☐ No ☒ N/A
Package type term 21 CFR 201.5	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: A February 6, 2017 meeting occurred with representatives from DMEPA, DBRUP, OBP (quality and labeling reviewers) to discuss the package type term. It was decided to maintain the package type term "single-use" due to concerns of confusion with using "single-dose" when 2 co-packaged prefilled syringes (PFS) are required to achieve the intended dose. December 12, 2018: This single-use terminology issue was also discussed at an internal labeling meeting and DBRUP and DMEPA still agreed to label the product as single-use instead of using the term single-dose.	
Drugs **Misleading statements** 21 CFR 201.6	☐ Yes ☒ No ☐ N/A
Strength 21 CFR 201.10 21CFR 201.100	✓ Yes ☐ No ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	✓ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

Usual dosage statement 21 CFR 201.55 21 CFR 201.100 Partial Label	☐ Yes ☐ No ☒ N/A
Inactive ingredients 21 CFR 201.100 Partial Label	☐ Yes ☐ No ☒ N/A
Storage requirements Partial Label	☐ Yes ☐ No ☒ N/A
Dispensing container 21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Package Label[5] Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	✓ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Lot number or other lot identification 21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Preservative 21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Number of containers 21 CFR 610.61	✓ Yes ☐ No ☐ 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.

Comment/Recommendation:

Strength/volume
21 CFR 610.61
21 CFR 201.10
21 CFR 201.100

✓ Yes
☐ No
☐ N/A

Comment/Recommendation:

Please include the expression of strength "105 mg/1.17 mL" on both panels and near the proprietary name, proper name and dosage formulation.

Delete the reference (b) (4) in the colored circle as it can be confused for the strength of one prefilled syringe. As an alternative, consider revising the images with the prefilled syringes and colored circle with the reference t (b) (4). Consider displaying an image of a prefilled syringe with the strength, 105 mg/1.17 mL, in a shape (e.g. square) + another image of a prefilled syringe with the strength, 105 mg/1.17 mL, in the same shape and color = a colored circle with the expression of the dose "210 mg/2.34 mL".

Two prefilled syringes were also required for one dose with Aimovig injection, BLA 761077, and the sponsor is Amgen, so a similar labeling format was recommended for this product.

January 14, 2019:
Amgen accepts the proposed revisions to remove th (b) (4); add a circle containing the strength, 105 mg/1.17 mL, above both syringes; and to add "= 210 mg/2.34 mL," in a contrasting colored circle.

The applicant's revisions are acceptable.

Storage temperature/requirements
21 CFR 610.61

✓ Yes
☐ No
☐ N/A

Comment/Recommendation:
This product should be administered by a healthcare provider. Thus, consider revising the last instruction in the alternate storage statemen (b) (4) (b) (4) to read similar to "Use the space below to write a new expiration date, 30 days from the date removed from the refrigerator." Also include in or to the left of the white expiration box the statement "Discard after".

January 14, 2019:
Amgen accepts the proposed revisions to the storage statement to read "Use the space below to write a new expiration date, 30 days from the date removed from the refrigerator". Additionally, Amgen added a "Discard after" statement.

The applicant's revisions are acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent
(21 CFR 610.61)

✓ Yes
☐ No
☐ N/A

Multiple dose containers (recommended individual dose) 21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Known sensitizing substances 21CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the inactive ingredient statement to read: "Each single use prefilled syringe delivers 1.17 mL of solution containing 105 mg of romosozumab, acetate (3.8 mg), calcium (0.61 mg), polysorbate 20 (0.07 mg) and sucrose (70 mg) in Water for Injection, USP, and sodium hydroxide to a pH of 5.2." The statement includes revising the list of inactive ingredients in alphabetical order per USP Chapter <1091> Labeling of inactive ingredients in alphabetical order. January 14, 2019: Amgen accepts the proposed revision to the inactive ingredient statement per USP Chapter <1091> Labeling of inactive ingredients in alphabetical order. The applicant's revisions are acceptable.	
Source of the product 21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Minimum potency of product 21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Rx only 21CFR 610.61 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Distributor 21 CFR 610.64	☐ Yes ☐ No ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
Preparation instructions 21 CFR 201.5	✓ Yes ☐ No ☐ N/A
Package type term 21 CFR 201.5	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: A February 6, 2017 meeting occurred with representatives from DMEPA, DBRUP, OBP (quality and labeling reviewers) to discuss the package type term. It was decided to maintain the package type term "single-use" due to concerns of confusion with using "single-dose" when 2 co-packaged prefilled syringes (PFS) are required to achieve the intended dose. December 12, 2018: This single-use terminology issue was also discussed at an internal labeling meeting and DBRUP and DMEPA still agreed to label the product as single-use instead of using the term single-dose.	
Drugs **Misleading statements** 21 CFR 201.6	✓ Yes ☐ No ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Spanish-language (Drugs) 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Net quantity 21 CFR 201.51	✓ Yes

	☐ No ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Dispensing container 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the first sentence of Medication Guide statement to read "ATTENTION: Provide the enclosed Medication Guide to each patient". to help enforce that an action is required by the healthcare provider. January 14, 2019: Amgen accepts the proposed revision to the first sentence of the Medication Guide. The applicant's revisions are acceptable.	
Other	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	

Prescribing Information and Medication Guide Evaluation

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	✓ Yes ☐ No ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	

A February 6, 2017 meeting occurred with representatives from DMEPA, DBRUP, OBP (quality and labeling reviewers) to discuss the package type term. It was decided to maintain the package type term "Single-use" due to concerns of confusion with using "single-dose" when 2 co-packaged prefilled syringes are required to achieve the intended dose.

December 12, 2018:
This single-use terminology issue was also discussed at an internal labeling meeting and DBRUP and DMEPA still agreed to label the product as single-use instead of using the term single-dose.

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION
21 CFR 201.57(c)(3)

✓ Yes
☐ No
☐ N/A

Comment/Recommendation:

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

✓ Yes
☐ No
☐ N/A

Comment/Recommendation:
Dr. Sun confirmed the proposed identifying characteristics were accurate.

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))

✓ Yes
☐ No
☐ N/A

Comment/Recommendation:

1st paragraph discusses the drug substance and includes:

OBP Labeling: To Applicant: Revised to include the cell line, pharmacological class and production method per 21 CFR 201.57(c)(12).

The sentence "Romosozumab is a sclerostin inhibitor produced in a mammalian cell line (Chinese Hamster Ovary) by recombinant DNA technology" was added to the first paragraph.

2nd paragraph discusses the drug product

OBP Labeling: To Applicant: Revised to list the inactive ingredients in alphabetical order per USP Chapter <7> Labeling and USP Chapter <1091> Labeling of inactive ingredients in alphabetical order.

The last paragraph was revised to read: Two 105 mg/1.17 mL single-use prefilled syringes are required to administer the recommended 210 mg dose of EVENITY. Each single-use prefilled syringe delivers 1.17 mL of solution containing 105 mg of romosozumab, acetate

(3.8 mg), calcium (0.61 mg), polysorbate 20 (0.07 mg) and sucrose (70 mg) in Water for Injection, USP, and sodium hydroxide to a pH of 5.2.

March 15, 2019: The applicant accepted all the proposed changes described above. The applicant's revisions are acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

OBP Labeling: To applicant: Deleted [redacted] (b) (4).
The reader is informed above to store the product in the carton to protect from light.

Dr. Chen confirmed the handling conditions, protect from light, do not shake, do not freeze, are accurate. Dr. Chen also confirmed the normal storage condition is under refrigeration, but the product can be stored at room temperature for up to 30 days.

Dr. Chen confirmed the prefilled syringe is not made with natural rubber latex. The applicant has requested including this statement in the prescribing information which is acceptable.

March 15, 2019: The applicant delete [redacted] (b) (4). The applicant's revision is acceptable.

MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

STORAGE AND HANDLING	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Med Guide contains the appropriate storage conditions

INGREDIENTS	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Med Guide revised to list inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients.
The Med Guide submitted on March 20 revised the order of the inactive ingredients. The applicant's revision is acceptable.

MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1 **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on March 15,2019)
  \\cdsesub1\evsprod\bla761062\0072\m1\us\draft-labeling-text-uspi.docx

- Medication Guide (submitted on March 20, 2019)
  \\cdsesub1\evsprod\bla761062\0073\m1\us\draft-medication-guide.doc

- Container Labels (submitted on January 14, 2019)

(b) (4)

- Carton Labeling (submitted on February 14, 2019)

(b) (4)

Scott Dallas

Digitally signed by Scott Dallas
Date: 3/28/2019 02:18:04PM
GUID: 508da712000294048aa136a18a6af06a

Chen Sun

Digitally signed by Chen Sun
Date: 3/28/2019 03:07:48PM
GUID: 508da6d60002626468c6cf7957ba189c

First Approval for Indication

Recommendation:
BLA: Approval

BLA 761062
Review #1
Review Date March 21 2017

Drug Name/Dosage Form	EVENITY™ (romosozumab) Pre-filled syringe
Strength/Potency	90 mg/mL solution in a single-use prefilled syringe
Route of Administration	Subcutaneous Injection (2 injections monthly)
Rx/OTC Dispensed	Rx
Indication	Treatment of osteoporosis in postmenopausal women at increased risk of fracture.
Applicant/Sponsor	Amgen
US agent, if applicable	N/A

Product Overview

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Chen Sun	OBP/DBRRII
Drug Product	Chen Sun	OBP/DBRRII
Immunogenicity	Chen Sun	OBP/DBRRII
Facilities	Michael Shanks	OPF/DIA
Microbiology	DMA-DS: Bo Chi DMA-DP: Lakshmi Narasimhan	OPF/DMA
Regulatory Business Process Manager	Melinda Bauerlien	OPQ/OPRO
Team Lead	Joel Welch	OBP/DBRRII
Application Technical Lead	Joel Welch	OBP/DBRRIV
Review Chief	Juhong Liu	OBP/DBRRII

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
Regulatory Project Manager	Samantha Bell	OND/ODEIII/DBRUP
Medical Officer	Dubuene Chang	OND/ODEIII/DBRUP
Pharm/Tox	Gemma Kuijpers	OND/ODEIII/DBRUP
Clinical Pharmacology	Lin Zhou	OTS/OCP/DCPIIII
Pharmacometrics	Fang Li	OTS/OCP/DCPIIII
Statistics	Jia Guo	OTS/OB/DBIII

a. Names
   i. Proprietary Name: **EVENITY™**
   ii. Trade Name: **EVENITY™**
   iii. Non-Proprietary/USAN: romosozumab
   iv. CAS name: 909395-70-6
   v. Common name: AMG 785
   vi. INN Name: romosozumab
   vii. Compendial Name: N/A
   viii. OBP systematic name: MAb Human (IgG2) ANTI Q9BQB4 (SOST_HUMAN)[AMG785]

b. Pharmacologic category
   Human IgG2λ monoclonal antibody

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761062/0.00	July 19, 2016
761062/0.07	October 11, 2016
761062/0.11	October 28, 2016
761062/0.12	November 23, 2016
761062/0.14	December 22, 2016
761062/0.15	January 10, 2017
761062/0.17	January 17, 2017
761062/0.19	January 30, 2017
761062/0.23	February 16, 2017
761062/0.25	February 22, 2017
761062/0.31	March 6, 2017
761062/0.32	March 7, 2017
761062/0.34	March 17, 2017

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

	TYPE			CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	N/A	N/A	N/A
	V			3	N/A	N/A	N/A
	V			3	N/A	N/A	N/A
	V			1	Adequate with Information Request	N/A	Reviewed by L. Narasimhan
	III			3	N/A	N/A	N/A
	III			3	N/A	N/A	N/A
	V			1	(b) (4)	N/A	Reviewed by L. Narasimhan
	V			3	N/A	N/A	N/A

(b) (4)		(b) (4)				
	III		3	N/A	N/A	N/A

n codes fo ows: 2 – Re ation; 4 – A "Comments")

Other codes indicate why the DMF was not reviewed, since last review; 3 – Sufficient information in ; 5 – DMF not available;6 – Other (explain under

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH (GHDB) – PFS Performance	July 19, 2017	Complete Jan 13 2017	Approval	Sarah Mollo

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The recommendation from the Office of Pharmaceutical Quality, CDER, is approval of STN 761062 for EVENITY™ (romosozumab) manufactured by Amgen, Inc. The data submitted in this application support the conclusion that the manufacture of EVENITY™ is well controlled and produces 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.

b. Action letter language

- Manufacturing location:
  - Drug substanc (b) (4)
  - Drug product –
- Dating period:
  - Drug product – 36 months; 2-8 ºC
  - Drug substance (b) (4)
  - Stability option
    - For stability protocols:
      - None
- Exempt from lot release
  - Yes
- Exempt specified according to 601.2a

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following PMC is proposed to the sponsor. The goal of this PMC study is to (b) (4)

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management. For additional information see the source technical document from the Office of Biotechnology Products and the Product Quality Microbiology Reviews from the Division of Microbiological Assessment.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
High Molecular Weight (HMW) Impurities	Potency and immunogenicity	Originate in production bioreactor. May increase during storage of DS and DP. Increase is expected after exposure to heat and light	(b) (4)	N/A

			(b) (4)	
Low Molecular Weight (LMW) Species (b) (4)	Potency, PK and immunogenicity.	Originate in the production bioreactor. LMW can be formed by non-enzymatic fragmentation or cleavage of protein backbone		N/A

			(b) (4)	
Glycosylation (*N*-Glycan profile) Romosozumab s glcoyslated (b) (4) (b) (4)	This attribute can impact biological activity, PK and safety. (b) (4)	These modifications occur in the cell culture process. It does not change during DS or DP storage.		N/A
Charge Isoforms (b) (4)	Biological activity and safety.	These modifications most likely occur during the cel culture process. Minima increase is observed during DS and DP manufacture and storage.		N/A

(b) (4) Sequence variants are also observed present in basic fraction. .		(b) (4)	
(b) (4)	This could impact biologica activity, PK, safety, and efficacy.		N/A
(b) (4) isoform composition	This could impact biologica activity, and efficacy.		N/A

Sequence Variants	This could impact PK, efficacy, and immunogenicity	Likely due to cell bank, though no definite cause is known.	(b) (4)	N/A

B. Romosozumab Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes.

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Host Cell Proteins (HCP)	Safety nd immunogenicity	(b) (4)		N/A
Host Cell DNA	Safety			N/A

		(b) (4)	
(b) (4)	Safety, PK, nd immunogenicity		N/A
	Safety nd immunogenicity		N/A
	Safety nd immunogenicity		N/A

		(b) (4)	
Insulin Like Growth Factor (IGF-1)	Safety nd immunogenicity		N/A
(b) (4)	Safety		N/A
(b) (4)	Safety		N/A
Bioburden	Safety, Purity, and Efficac (degradation or modification of the product by contaminating		N/A

	microorganisms	(b) (4)	
Endotoxin	Safety and Purity		N/A
Viruses	Safety		N/A

Mycoplasma	Safety	(b) (4)	N/A
pH	General CQA: Safety and efficacy		N/A
Protein Concentration	General CQA: Safety and efficacy		N/A
Appearance: color	General CQA: Safety and efficacy		N/A
Appearance, Clarity/	General CQA: Safety and		N/A

Opalescence	efficacy	(b) (4)	
Osmolality	Safety		N/A
Polysorbate 20	Safety and efficacy		N/A
Identity	Safety and efficac		
Leachables/extractables	Safety and efficacy (indirect effects n stability)		N/A

			(b) (4)	

a. Description

Romosozumab is a humanized monoclonal antibody (mAb) of the IgG2k isotype that binds sclerostin. It has a molecular weight of approximately 149 kDa.

b. Mechanism of action

Romosozumab binds to and blocks the activity of sclerostin, which is regulatory factor in bone metabolism. Sclerostin acts by binding the low-density lipoprotein receptor-related proteins (LRP4, LRP5, and LRP6), resulting in inhibition of Wnt signaling and reduction osteoblast mediated bone formation. Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption.

c. Potency Assay

The potency method is a cell based assay using a murine osteoblast cell line (MC3T3E1) that expresses three separate genes (a luciferase reporter gene, human Wnt-1, and Tet repressor protein). The assay measurement is based on production of luciferase in response to Wnt-1 signal. The cells are treated with a fixed concentration of sclerostin, addition of romosozumab leads to a dose-dependent increase in the luciferase production. The reaction of luciferase with substrate results in luminescence which is measured using a luminometer. Three individual plates are prepared for each assay run. The sponsor reports the potency as relative % to the reference material.

d. Reference material(s)

(b) (4)

e. Critical starting materials or intermediates

Cell Banks: Romosozumab is produced from a recombinant DNA-derived CHO cell line using standard cell culture techniques. (b) (4)

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

(b) (4)

g. Container closure
The container closure system is a (b) (4) container sealed with a (b) (4) cap closure (b) (4) (b) (4).

h. Dating period and storage conditions
The data provided in the BLA support the establishment of a shelf life o (b) (4) months for romosozumab drug substance when stored at (b) (4)

C. Drug Product [Evenity™] 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 Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility	Safety	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)	N/A
Endotoxin	Safety, purity and potential immunogenic reactions	Contaminants could be introduced throughout DP manufacturing or due to integrity failure of the		N/A

		container closure.	(b) (4)	
Particulate matter (sub-visible)	Safety and Immunogenicity	Sub-visible particulates could form throughout manufacturing or on storage. Might contain product- and process-related impurities.		N/A
Appearance -Visible particulates	Safety and efficacy	Visible particulate might be affected by the manufacturing process and storage conditions.		N/A
Appearance – Color, Clarity and degree of opalescence	Safety and efficacy	Manufacturing process, formulation, and storage conditions		N/A

pH	Safety and efficacy	pH is impacted by formulation. No change on stability is expected.	(b) (4)	N/A
Osmolality	Safety	Osmolality is impacted by formulation. No change is expected on stability.		N/A
Polysorbate 20	Safety and efficacy	Level of Polysorbate 20 excipient is impacted by formulation. No changes are expected on stability.		N/A
Protein Concentration	Safety and efficacy	Protein concentration is impacted by formulation during DP manufacturing and might be impacted by		N/A

		storage conditions.	(b) (4)	
Identity	Safety and efficacy	General CQA		N/A
Container closure integrity (sterility assurance)	Safety	CQA		N/A
Leachables/extractables	Safety	Process-related leachables and extractables could potentially be introduced by any product contact equipment, containers and consumables.		N/A

a. Potency and Strength: Each single-use prefilled syringe with a deliverable volume of 1.17 mL contains 105 mg of EVENITY (90 mg/mL).

b. Description/Commercial Image: Carton of two 90 mg/mL single-use prefilled syringes. EVENITY is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution for subcutaneous injection.

c. List of Excipients:
Each single-dose (two single-use prefilled syringes) contains 210 mg romosozumab i (b) (4) solution for a concentration of 90 mg/mL. Each 1.17 mL of solution contains 105 mg romosozumab, calcium (0.61 mg), acetate (3. (b) (4) mg), sucrose (70 mg), polysorbate 20 (0.07 mg), sodium hydroxide (b) (4) (b) (4) and Water for Injection. The pH of the solution is 5.2.

d. Reference material(s) Same as drug substance

e. Manufacturing Process: EVENITY drug product is manufactured at (b) (4) (b) (4)

f. Container Closure: The primary container closure consists of (b) (4) (b) (4) syringe with an (b) (4) needle covered with an (b) (4) needle shield and a (b) (4) (b) (4) plunger-stoppe (b) (4) (b) (4)

g. Expiration Date & Storage Conditions; The stability data in the BLA support a shelf life of 36 months for EVENITY drug product when stored at the recommended storage condition of 2 - 8°C.

h. List of co-packaged components, if applicable: N/A

B. Novel Approaches/Precedents

None

C. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C

Protect from light

Do not freeze

Do not shake

D. Establishment Information

A pre-licensed inspection was performed January 30 – February 3 2017 at the ARI facility. The DP site inspection was waived. The recommendation is for approval. A description is found below for each individual site. For additional information, see the review from the Division of Inspectional Assessment.

OVERALL RECOMMENDATION: Approval					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
DS manufacture, DS in-process, lot release and stability testing, working cell bank storage.	(b) (4)		A Preapproval inspection (PAI) in support of this subject BLA was conducted (b) (4) by CDER OBP and DIA.	The investigators recommended voluntary actions indicated (VAI) for qualification, laboratory records and quality issues. Final compliance decision: Approve	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
DS master cell bank and working cell bank storage, working cell bank production.			The most recent inspection was a limited GMP inspection that was conducted in response to two Risk Evaluation and Mitigation	No observations issued during most recent inspection.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.

			Strategies (REMS) Inspection Assignment Memorandums (b) (4) The inspection resulted in NAI and approved decision.		
DS lot release and stability testing.	(b) (4)		The most recent inspection was conducted by CDER OBP and DIA, and ORA (b) (4) and resulted in VAI with an approved decision.	The investigators recommended voluntary actions indicated (VAI) for PPQ procedures and microbial quality issues. Final compliance decision: Approve	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
DS unprocessed bulk mycoplasma and adventitious viral testing.			The most recent inspection was conducted on (b) (4) and resulted in NAI with an	No observations issued during most recent inspection.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.

			approved decision.		
DS lot release and stability testing	(b) (4)		The most recent inspection was conducted on (b) (4) and resulted in VAI with an approved decision.	The investigators recommended voluntary actions indicated (VAI) for quality issues. Final compliance decision: Approve	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Drug product manufacturing sterility, identity, visual inspection, and compendia raw materials and/or excipient testing	(b) (4)		The most recent inspection was conducted on (b) (4) and resulted in VAI with an approved decision.	The investigators recommended voluntary actions indicated (VAI) for validation, Laboratory controls, stability, and quality control issues. Final compliance decision: Approve	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
Drug product lot release and stability testing			A Preapproval inspection (PAI) in support of this subject BLA was conducted (b) (4)	The investigators recommended voluntary actions indicated (VAI) for qualification, laboratory records	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.

			(b) (4) by CDER OBP and DIA.	and quality issues. Final compliance decision: Approve	
Drug product lot release and stability testing, packaging and labeling, distribution.	Amgen Manufacturing Limited Rd. 31 Km 24.6 Juncos, PR	1000110364	The most recent inspection was conducted by CDER OBP and DIA, and ORA (b) (4) and resulted in VAI with an approved decision.	The investigators recommended voluntary actions indicated (VAI) for PPQ procedures and microbial quality issues. Final compliance decision: Approve	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
Drug product container closure integrity for stability testing.	(b) (4)		The most recent inspection was conducted on (b) (4) and resulted in NAI with an approved decision. ,	No observations issued during most recent inspection.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
Drug product lot release and stability testing.	Amgen Technology Pottery Rd. Dublin, Dun Laoghaire, Ireland	3002808497	The most recent inspection was conducted on (b) (4) and	The investigators recommended voluntary actions indicated (VAI) for quality issues. Final compliance	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.

			resulted in VAI with an approved decision.	decision: Approve	

E. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved: Annual GMP stability protocol. Concurrent validation protocol for resin reuse. Qualification of new reference standard (primary and secondary).

ii. Outstanding review issues/residual risk

iii. Future inspection points to consider: Evaluation of trending program to evaluate sequence misincorporation in drug substance batch manufacture.

b. Drug Product

i. Protocols approved: Annual GMP stability protocol.

ii. Outstanding review issues/residual risk

iii. Future inspection points to consider: None

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 Sourced		x	
9.	Transgenic Plant Sourced		x	
10.	New Molecular Entity	x		
11.	PEPFAR Drug		x	
12.	PET Drug		x	
13.	Sterile Drug Product	x		

14.	Other_____			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		x	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements tem)		x	
18.	SPOTS (Special Products On-line Tracking System		x	
19.	USAN Name Assigned	x		
20.	Other_____		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			
27.	Real Time Release Testing (RTRT)		x	
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 _____			x	

Chen Sun

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Juhong Liu

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