CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125522Orig1s000

CHEMISTRY REVIEW(S)

Johnson, Kati

om: Shanks, Michael
ent: Wednesday, August 26, 2015 8:32 AM
To: Johnson, Kati
Subject: 125552

Overall Manufacturing Inspection Recommendation

Task Details | Document Management | Updates | Issues | **Inspection Management Form**

Inspection Management Form

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BLA 125522-Orig1-New/BLA(1)

(b) (4) CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) | Approve Facility - 2015-

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility - 2015-12-03

AMGEN INC | 2026154 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility - 2015-12-30

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility - 2016-03-22

AMGEN MANUFACTURING LIMITED | 1000110364 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility - 2017-01-2

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility - 2017-05-14

(b) (4) CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) | Approve Facility - 2

AMGEN INC | 2026154 | (b) (4) -

(b) (4) - FACILITY PROFILE CANCELLED

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Overall Manufacturing Inspection Recommendation

(●) Approve
( ) Withhold

Overall Application Re-evaluation Date
8/28/15

Cancel

Mike

chael Shanks, Biologist
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

BLA STN 125522

REPATHA™ (Evolocumab)

Amgen Inc

Bazarragchaa Damdinsuren, MD, PhD, Quality Reviewer (Drug Substance)
Sang Bong Lee, PhD, Quality Reviewer (Drug Product)
Chana Fuchs, PhD, Team Lead

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

OBP CMC Review Data Sheet

1. BLA#: STN 125522

2. LEGAL BASIS FOR SUBMISSION: 351(a)

3. REVIEW DATE: July 15, 2015

4. PRIMARY REVIEW TEAM:

Medical Officer:	Eileen Craig
Pharm/Tox:	Calvin Lee Elmore
Product Quality Team:	Bazarragchaa Damdinsuren, Quality Reviewer (DS) Sang Bong Lee, Quality Reviewer (DP) Chana Fuchs, Team Lead
BMT or Facilities:	Michael Shanks (DS), Lakshmi Narasimhan (DP)
Clinical Pharmacology:	Suryanarayana Sista, Justin Earp
Statistics:	Susie Sinks
OBP Labeling:	Jibril Abdus-Samad
RPM:	Kati Johnson

5. MAJOR GRMP DEADLINES

Filing Meeting: 10/8/2014
Mid-Cycle Meeting: 2/12/2015
Wrap-Up Meeting: 5/28/2015
Primary Review Due: 6/01/2015
Secondary Review Due: 6/08/2015
PDUFA Action Date: 8/27/2015

6. COMMUNICATIONS WITH SPONSOR AND OND:

Communication/Document	Date
CMC Pre-BLA Meeting	1/24/2014
Filing review memo	10/22/2014
Information Request #1	2/11/2015
Information Request #2	4/02/2015
Information Request #3	5/19/2015
Information Request #4	6/12/2015
Information Request #5	6/19/2015
Teleconference #1	6/24/2015
Information Request #6	7/01/2015

7. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 125522/0	8/27/2014	yes
STN 125522/22 (response to microbiology reviewer IR)	1/12/2015	yes
STN 125522/27 (response to IR #1)	3/02/2015	yes
STN 125522/42 (response to IR #2)	4/21/2015	yes
STN 125522/56 (response to IR #3)	6/01/2015	yes
STN 125522/67 (response to IR #4)	6/22/2015	yes
STN 125522/69 (response to IR #5)	6/24/2015	yes
STN 125522/70 (response to Teleconference #1)	6/26/2015	yes
STN 125522/71 (response to IR #6)	7/08/2015	yes

8. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Repatha
b. Trade Name: Repatha
c. Non-Proprietary/USAN: Evolocumab
d. INN Name: Evolocumab
e. Common name: AMG 145
f. OBP systematic name: (b) (4)

9. PHARMACOLOGICAL CATEGORY: Therapeutic recombinant human IgG2 monoclonal antibody

10. DOSAGE FORMS: 140 mg Repatha (evolocumab) single-use prefilled syringe, injection
140 mg single-use prefilled Repatha (evolocumab SureClick® Autoinjector, injection)

11. STRENGTH/POTENCY:

(i) The concentration/strength of the Drug Product: 1 ml of a 140 mg/mL solution of evolocumab
(ii) Type of potency assay(s): Receptor-ligand binding assay (product specific, proprietary)

12. ROUTE OF ADMINISTRATION: subcutaneous injection

13. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

[redacted] (b) (4)			yes	No review of the DMF required as all the relevant information related to compatibility with the product was in the BLA
			yes	No review required as all the relevant information related to compatibility with the product was in the BLA
21000	Amgen	[redacted] (b) (4) Processing Warehousing and Laboratories at AML site	yes	This DMF was lastly reviewed on 02/01/2012 by the microbiology reviewer Steven Fong (DMA). The AML facility was inspected by DMA with the district on 03/24/2014 and the inspection was VAI.

14. INSPECTIONAL ACTIVITIES

There were one pre-license inspection (PLI) at the evolocumab drug substance manufacturing facility [redacted] (b) (4) and one at drug product manufacturing facility (ATO).

Inspection of [redacted] (b) (4) as conducted on [redacted] (b) (4) by facility reviewers Steven Fong (Lead Investigator), Wayne Seifert, Michael Shanks and OBP reviewers Bazarragchaa Damdinsuren and Chana Fuchs. This manufacturing facility is responsible for the manufacturing of evolocumab drug substance, [redacted] (b) (4) A 483 with one observation was issued at the end of inspection. The observation is:

[redacted] (b) (4)

The sponsor provided response on April 02, 2015. Final compliance status is pending at time of this review.

Inspection of the drug product manufacturing site at Amgen, Inc. (Thousand Oaks, CA; also referred to as Amgen Thousand Oaks [ATO]) facility was conducted on May 4-22, 2015 by Carla Lundi (Lead inspector) and Jennifer Gogley from the LOS-DO. This was a comprehensive inspection of a sterile parenteral clinical biologics drug product for human use conducted under

FACTS inspection assignment 11520121 for a GMP inspection and product specific PLI coverage of evolocumab under the current BLA. A FDA 483 with three observations was issued at the end of inspection. The high level points of the observations were as follows:

a. Written records of investigations into unexplained discrepancies do not always include the conclusion and follow-up.
b. (b) (4) processing areas are deficient regarding the system for monitoring environmental conditions.
c. Laboratory records do not include a statement of each method used in the testing of a sample, and it is difficult to trace which technology is used.

Inspection of the drug product manufacturing site at Amgen Manufacturing Ltd (AML; Juncos, Puerto Rico) facility building (b) (4) was waived based on the the relatively less complex process for manufacturing of the DP in conjunction with the fact that AML (b) (4) has been approved to manufacture multiple licensed products (b) (4) as well as the recent compliance history [last inspection under the CPs relevant to the evolocumab DP manufacturing, specifically # 7356002 – Drug Process Inspection (with coverage of the Quality, Facilities and Equipment, Materials, Labeling and Packaging, Production, and Laboratory Control Systems and # 7356.002A – Sterile Drug Process Inspection on1/12-23/2015, resulting in a VAI status) and the current GMP status.

14. CONSULTS REQUESTED BY OBP: The device reviews for both the PFS and the AutoInjector were done by CDRH. Consult request was processed by OND.

15. QUALITY BY DESIGN ELEMENTS

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

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

DOE studies were submitted in support of formulation development and assessment of control strategies for DS and DP manufacturing. Sponsor conducted risk assessments for the DS and DP manufacturing processes using FMEA. Each of the operational parameters was scored based on risk severity (S), frequency of occurrence (O), and detectability of variability in the operating range (D). The resulting RPN scores were compared to a predetermined threshold to assess overall potential risk. Parameters with a low RPN score were classified as non-key and not evaluated further during process characterization. Prior knowledge from other products developed and manufactured by Amgen was also used in the FMEA assessment and in support of the overall control strategy of evolocumab.

16. PRECEDENTS: None.

17. PROTOCOLS APPROVED WITHIN THE BLA

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(b) (4)

19. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Michele Dougherty, Ph.D. Review Chief Division of Biotechnology Research and Review IV	
Chana Fuchs, Ph.D. Team Leader Division of Biotechnology Research and Review IV	
Primary Reviewers: Bazarragchaa Damdinsuren, M.D., Ph.D. Senior Staff Fellow Division of Biotechnology Research and Review IV	
Sang Bong Lee, Ph.D. Quality Reviewer Division of Biotechnology Research and Review IV	

B. CC Block

Recipient	Date
Clinical Division BLA RPM Kati Johnson CDER/ODEII/DMEP	
Division of Biotechnology Research and Review IV File/BLA STN 125522	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation
The data submitted in this Biologics License Application support the conclusion that the manufacture of Repatha™ (evolocumab) 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 sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Repatha™ (evolocumab) be approved for human use (under conditions specified in the package insert).

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements:

1) To establish the evolocumab drug substance (DS) stability acceptance criteria for the 9 and 12 months stability timepoints at the (b) (4)°C condition based on available stability data. The acceptance criteria and supporting data will be submitted as a CBE.

2) To demonstrate that the identity by ELISA assay performed at Amgen Thousand Oaks (ATO) for evolocumab drug product (DP) lot release testing functions within the parameters identified for the validated assay prior to releasing evolocumab lots tested for identity at ATO. The study report will be submitted as a CBE-30.

3) To re-evaluate the evolocumab DS (b) (4) limits (b) (4) The final report should include the corresponding data, the analysis and statistical plan used to evaluate (b) (4) limits, and any proposed changes to the limits.

4) To re-evaluate the evolocumab DP acceptance criteria for (b) (4) as specified in PMC 3. The DP lots will include the lots which were used in the analysis of specifications submitted in the BLA and subsequent DP lots manufactured. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the (b) (4) limits, and any proposed changes to the limits. The analysis should also include linkage to the DS (b) (4) limits for (b) (4) based on the re-evaluation specified in PMC 3.

5) To re-evaluate the evolocumab DP release and stability acceptance criteria for the PFS and AI presentations after the manufacture of DP lots from an additional 2 DS manufacturing campaigns. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the results and acceptance criteria, and any proposed changes to the criteria.

IV. Review of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Amgen claims categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(c), 21 CFR 25.34(b). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review

The carton and container labels were reviewed and found to be acceptable with additional changes with recommendations from OBP. The OBP carton and container labeling review is uploaded as a separate file in Panorama.

VI. Review of Common Technical Document - Quality Module 3.2 and module 2.3, Quality Overall Summary. The review of Module 2.3 and 3.2 are included in this review.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

(b) (4)

[redacted]

BLA EDR Location: Application 125522

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

2.3 – QUALITY OVERALL SUMMARY

Review of the QOS did not identify anything that was not included in Module 3. Therefore, all information will be covered in Module 3. It should be noted that as of finalization of this review, although many updates have occurred to Module 3, the matching updates have not yet been implemented in Module 2.3.

S. DRUG SUBSTANCE

[This section is reviewed by Bazarragchaa Damdinsuren]

3.2.S.1 General information

Evolocumab is a human monoclonal immunoglobulin IgG2 that specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) with picomolar affinity and prevents its interaction with the low density lipoprotein receptor (LDLR). The epitope targeted by evolocumab spans the interaction domain of PCSK9 with repeat A of the epidermal growth factor homology (EGF-A) domain of the LDLR.

Evolocumab's Amgen code name is AMG 145, CAS registry number - 1256937-27-5.

3.2.S.1.2 Structure

Evolocumab consists of 2 heavy chains (HC) and 2 light chains (LC) of the lambda subclass.

(b) (4)

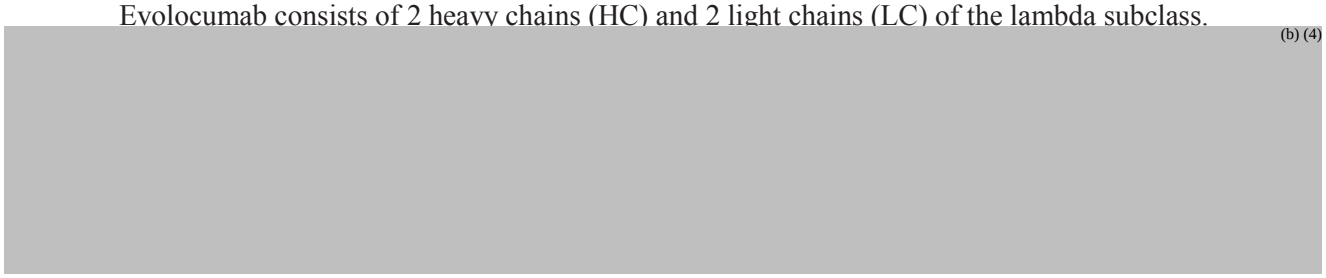

Figure 2: Encoded primary amino acid sequence of evolocumab:

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3.2.S.1.3 General Properties

Table 1. Physical and Chemical Properties of Evolocumab

Immunoglobulin subclass	IgG2
Sequence	Human sequence
Biological target	Specific binding to human PCSK9
Physical description	Clear to opalescent; colorless to yellowish; liquid, practically free from particles
Molecular mass[a]	(b) (4)
Cysteines	(b) (4)
Number of disulfide bonds	18
Glycosylation	(b) (4)
Extinction coefficient	Theoretical: (b) (4) Determined:
Isoelectric point (pI)	Theoretical: Determined:
T_m (melting temperatures)[c]	(b) (4)

[a] Experimentally determined molecular mass
[b] Theoretical isoelectric point with heavy chain C-terminal glycine
[c] Experimentally determined melting temperatures

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The facilities involved in the manufacture and testing of evolocumab drug substance (DS) and contract testing laboratories are listed in Tables 1 and 2.

Table 1. Drug Substance Facility Responsibilities

Facility	Address	Responsibility	US FDA Registration Number
(b) (4)	(b) (4)	Drug substance manufacture (b) (4) Drug substance in-process, lot release and stability testing Working cell bank storage	(b) (4)
Amgen Inc. (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320 USA	Master cell bank and working cell bank storage Working cell bank production	FEI: 2026154 DUNS: 039976196
Amgen Inc. Longmont Facility (Referred to as Amgen Colorado or ACO)	4000 Nelson Road Longmont, CO 80503 USA	Master cell bank and working cell bank storage	FEI: 3002892484 DUNS: 071629633
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA	Drug substance lot release and stability testing	FEI: 1000110364 DUNS: 785800020

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

Table 2. Contract Testing Laboratories

Facility	Address	Type of Testing	US FDA Registration Number
(b) (4)			

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

Reviewer comment: *(b) (4) and AML facilities are listed for DS release and stability testing. The method validation reports noted that the methods are validated at (b) (4) and AML sites (except for compendial methods). The BLA was not clear on which sites will be responsible for which tests. Therefore, an information request (IR) was sent to sponsor on 4/01/2015 requesting that they specify the tests used at each site. Sponsor responded on 4/20/2015 identifying that both (b) (4) and AML perform all the DS tests. Information related to DP testing sites is in section 3.2.P.3.1.*
In addition, on 4/01/2015 sponsor was asked to update the manufacturers sections with the specific building/site intended for the licensed evolocumab process. This updated Table 1 is included, above. In the initial submission, (b) (4) was included as a site for (b) (4) , however due to lack of information on the method validation sponsor removed the site from the Table 2 and form 356h (response to question 5 in IR dated 5/19/2015 in section 3.2.S.2.4).
(b) (4)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Reviewer comment: *In the initial BLA submission, the description of the manufacturing processes, including the process parameter ranges, were not sufficiently described with details that would ensure control of the manufacturing process. The following IR was communicated with the sponsor on 6/12/2015 to include details of the manufacturing process "*15. Update BLA sections 3.2.S.2.2 with detailed descriptions of each step in the evolocumab manufacturing process. Examples of details that should be incorporated into appropriate sections include: (b) (4)
Amgen responded on 6/19/2015 updating the requested details into the sections in 3.2.S.2.2., except (b) (4) I agree with the parameters included and with the reasoning of not including the above-described two parameters. The response is acceptable. The review included the updated documents.

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