

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125559Orig1s000

CHEMISTRY REVIEW(S)

First Approval for Indication Voucher Expedited

Recommendation: Approval

BLA/NDA 125559 Addendum July 17, 2015

Drug Name/Dosage Form	Praluent (alirocumab)/pre-filled syringe and pre-filled pen
Strength/Potency	75 mg/ml or 150 mg/ml
Route of Administration	Subcutaneous every 2 weeks
Rx/OTC Dispensed	Rx
Indication	Long term treatment of patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia
Applicant/Sponsor	Regeneron
US agent, if applicable	NA

Product Overview

Praluent (alirocumab) is a recombinant fully human monoclonal IgG1 antibody produced in CHO cells. Praluent inhibits binding of Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) to the Low Density Lipoprotein Receptor (LDLR) on the surface of hepatocytes. PCSK9 binding to the LDLR promotes LDLR degradation, whereas inhibition of PCSK9 binding leads to increased amounts of cell surface LDLR. Increased amounts of cell surface LDLR lead to reduced serum levels of LDL and related lipoproteins because LDLR binding and internalization is the main clearance mechanism for these lipoproteins. The IgG1 Fc domain of alicumab does not have effector function so the mechanism of action of Praluent is only by blocking PCSK9 binding to the LDLR. Praluent is proposed for the treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-cholesterol (LDL-C), total-C, non-high density lipoprotein (non-HDL) -C, Apolipoprotein B, triglycerides, and lipoprotein(a), and to increase HDL-C, and Apolipoprotein A either in combination with a statin or as a monotherapy.



QUALITY REVIEW BLA 125559 Praluent (alirocumab)



DISCIPLINE	REVIEWER	BRANCH/DIVISION	e-Signature
Drug Substance	Richard Ledwidge	Division of Biotechnology Review and Research III	Richard Ledwidge - S <small>Digitally signed by Richard Ledwidge S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2012.369707, cn=Richard Ledwidge S Date: 2015.07.21 13:12:54 -04'00'</small>
Drug Product	Richard Ledwidge	Division of Biotechnology Review and Research III	Richard Ledwidge - S <small>Digitally signed by Richard Ledwidge S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2012.369707, cn=Richard Ledwidge S Date: 2015.07.23 09:47:07 -04'00'</small>
Facilities	Michael Shanks	Division of Inspectional Assessment	Michael R. Shanks - S <small>Digitally signed by Michael R. Shanks S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2012.01408317, cn=Michael R. Shanks S Date: 2015.07.21 14:05:11 -04'00'</small>
Microbiology Drug Substance	Reyes Candau-Chacon	Division of Microbiology Assessment	Patricia F. Hughestroot - S <small>Digitally signed by Patricia F. Hughestroot S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130009.6547, cn=Patricia F. Hughestroot S Date: 2015.07.23 07:23:45 -04'00'</small>
Microbiology Drug Product	Colleen Thomas	Division of Microbiology Assessment	Colleen Thomas - S <small>Digitally signed by Colleen Thomas S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas S, 0.9.2342.19200300.100.1.1=200.0334597 Date: 2015.07.21 13:20:25 -04'00'</small>
DS and DP Team Lead	Howard Anderson	Division of Biotechnology Review and Research III	Howard A. Anderson - A <small>Digitally signed by Howard A. Anderson A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000.605508, cn=Howard A. Anderson A Date: 2015.07.21 14:51:56 -04'00'</small>
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	Zhihao Qiu - S <small>Digitally signed by Zhihao Qiu S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu S, 0.9.2342.19200300.100.1.1=20004.38274 Date: 2015.07.21 14:14:04 -04'00'</small>
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroot - S <small>Digitally signed by Patricia F. Hughestroot S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13000.96547, cn=Patricia F. Hughestroot S Date: 2015.07.23 07:23:15 -04'00'</small>
Application Technical Lead	Susan Kirshner	Division of Biotechnology Review and Research III	Susan L. Kirshner - S <small>Digitally signed by Susan L. Kirshner S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300.194629, cn=Susan L. Kirshner S Date: 2015.07.21 12:36:52 -04'00'</small>

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Pat Madara	ODE II/DMEP
Cross-disciplinary Team Lead	Mary Roberts	ODE II/DMEP
Medical Officer	James Smith	ODE II/DMEP
Medical Officer	Julie Golden	ODE II/DMEP
Pharm/Tox	Lee Elmore, Stephanie Leuenroth-Quinn	ODE II/DMEP
Clinical Pharmacology	Sang Chung, Jayabharathi Vaidyanathan	DCPII
Statistics	Brad McEvoy, Mark Rothmann	DBVI

- a. Names
 - i. Proprietary Name: Praluent
 - ii. Trade Name: Praluent
 - iii. Non-Proprietary/USAN: alirocumab
 - iv. INN Name: alirocumab
 - v. Other: REGN727
 - vi. OBP systematic name: [REDACTED] (b) (4)

- b. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 125559/0000	11/24/2014
STN 125559/0006	1/27/2015
STN 125559/0008	2/13/2015
STN 125559/0022	3/26/2015
STN 125559/0025	4/06/2015
STN 125559/0033	4/17/2015
STN 125559/0035	4/20/2015
STN 125559/0039	4/23/2015
STN 125559/0042	4/29/2015
STN 125559/0046	5/11/2015
STN 125559/0047	5/18/2015
STN 125559/0048	5/22/2015
STN 125559/0053	6/1/2015
STN 125559/0058	6/30/2015

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	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type V	(b) (4)	(b) (4)	3	N/A		
	Type III		3	N/A			
	Type V		3	N/A			
	Type III		1	Satisfactory	7/1/2015		
	Type III		2	Satisfactory	11/26/2013		
	Type III		1	Satisfactory	6/11/2015		

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 enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

3. CONSULTS: None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality recommends approval of STN 125559 for Praluent (alirocumab) injection, 75 mg and 150 mg, manufactured by (b) (4)

The data submitted in this application are adequate to support the conclusion that the manufacture of Praluent 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.

a. Benefit/Risk Considerations

Praluent is proposed for the treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-cholesterol (LDL-C), total-C, non-high density lipoprotein (non-HDL) -C, Apolipoprotein B, triglycerides, and lipoprotein(a), and to increase HDL-C, and Apolipoprotein A either in combination with a statin or as a monotherapy. High LDL-C is associated with increased risk for serious cardiovascular events, and other cholesterol lowering drugs such as statins are indicated for reducing the risk of serious cardiovascular events in some patients. Praluent was found to be effective in reducing LDL-C to very low levels (b) (4) in subjects who were concomitantly taking statins (b) (4). Therefore, Praluent may be used to treat currently unmet medical needs.

The DS manufacturing process is well controlled and should consistently deliver DS of desired quality. No DS related PMCs are requested.

The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. However, confirmatory information and minor method revisions for a number of product quality microbiology tests are needed to corroborate findings reported in the license application. Because information provided in the license application show that the applicant can consistently produce Praluent that is safe, pure, and potent the confirmatory studies may be conducted post licensure as Post Marketing Commitments (PMCs). Therefore, six PMCs are included with the approval of this application.

1. The sponsor provided microbial retention data (b) (4). The results met the acceptance criteria. (b) (4)

(b) (4)

2. The bioburden and sterility test methods were qualified with two lots of product. Bacteriostasis/fungistasis was not observed. Method qualification with three different lots of product is required for BLA products due to product complexity. However, because this manufacturing process appears to consistently yield comparable product, comparable method qualification results are expected for the third lot of product.

3. The (b) (4) is used for container closure integrity testing of drug product stability samples. The method was validated and shown to be capable

(b) (4)

The sponsor was asked to replace the current system suitability control

The goal of this change is to implement a system suitability control more appropriate for a test that is designed

4. Microbial control of the process was demonstrated during process validation. (b) (4) of product-contact equipment and components was reviewed and found satisfactory. Implementation of (b) (4)

(b) (4)

5. The drug product manufacturing site uses the (b) (4)

(b) (4)

6. The (b) (4) mL bioburden limit for (b) (4) considering that the drug substance bioburden specification is ≤ 1 CFU/10 mL. (b) (4)

The sponsor indicated that this limit was chosen based on the (b) (4)

(b) (4)

The goal of the study is to determine (b) (4) in-process bioburden limits are supported by process capability.

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

Below are PMCs negotiated with the applicant. The final numbering of the PMCs and the Report Submission dates can be found in the approval letter.

1. Repeat the microbial retention study [REDACTED] (b) (4)
[REDACTED]
Provide the data in a PMC study report.
2. Qualification of the bioburden and sterility test methods was performed with only two lots of drug product, with the exception of qualification of the sterility test method for the recovery of *A. brasiliensis*. As a post-marketing commitment, please provide bioburden and sterility test qualification data from one additional batch of 150 mg/ml drug product that was not manufactured from drug substance batches 8065000001 or 8065000002. The study may be done with bulk drug product. The data should be provided in the first annual report.
3. [REDACTED] (b) (4)
[REDACTED] Revise the container closure integrity test method to include a system suitability control with [REDACTED] Report this change in the first annual report. (b) (4)
4. Implement [REDACTED] (b) (4)
[REDACTED]
The hold time limits should be supported by the studies performed to fulfill PMC 5.
5. To confirm that reduced endotoxin recovery over time is not observed with the [REDACTED] (b) (4)
[REDACTED]
The study should be designed to support the proposed endotoxin testing [REDACTED] (b) (4)
6. Revise the [REDACTED] (b) (4)
[REDACTED] after data from additional drug product batches have been analyzed.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see Appendix A of the initial integrated review memo.

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

CQA	Risk	Origin	Control Strategy	Other
Potency	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Low Molecular Weight (LMW) Impurities				(b) (4)
(b) (4)				(b) (4)
High Molecular Weight (HMW) Impurities				(b) (4)
Charge Variants				(b) (4)

B. Drug Substance: Alirocumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see Appendix A and Appendix B of the initial integrated review memo.

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

COA	Risk	Origin	Control Strategy	Other
(b) (4)	(b) (4)	(b) (4)	(b) (4)	
	Patient safety	(b) (4)		
	Safety/immunogenicity	(b) (4)		
	Safety	(b) (4)		

			(b) (4)
pH	Safety and Efficacy	Formulation	
(b) (4)	Safety and Immunogenicity	(b) (4)	
	Safety		
	Efficacy		
Appearance Physical Form, Clarity, Color	Safety and Efficacy		

			(b) (4)
Identity	Safety and Efficacy	N/A	
Osmolality	Safety	Drug product formulation	
Polysorbate 20	Safety	Formulation	
Leachables	Safety	(b) (4)	

1. Description

Alirocumab is a fully humanized antibody that was generated by standard monoclonal antibody techniques and is expressed in Chinese Hamster Ovary (CHO) cells. (b) (4)

[Redacted]

For additional information see Appendixes A and C of the initial integrated review memo.

2. Mechanism of action

Soluble PCSK9 binds a low-density lipoprotein receptor (LDLR) and low-density lipoprotein complex. After internalization the ternary complex is shuttled to the lysosomal compartment for degradation. PCSK9-mediated LDLR degradation causes reduction of LDL-R levels and results in decreased LDL removal from the circulation and concomitantly higher serum LDL. Alirocumab binds PCSK9 with high affinity preventing PCSK9 binding to LDL-R. In the absence of PCSK9, the LDLR/ LDL complex dissociates after internalization, with LDL being shuttled to the lysosome while the LDLR is recycled back to the cell membrane. LDLR recycling causes an increase in LDL removal and a lowering of serum LDL and related lipoproteins. For additional information see Appendix A of the initial integrated review memo.

3. Potency Assay

Potency is defined as the percent activity relative to alirocumab reference standard. The potency assay is a cell-based assay that measures the uptake of fluorescently labeled LDL into human liver cell line HepG2/REGN727 and provides an indirect measure of alirocumab's ability to inhibit PCSK9-dependent LDLR degradation. The potency assay is suitable since it is highly relevant to the alirocumab mechanism-of-action and has acceptable precision. For additional information see Appendix A of the initial integrated review memo.

4. Reference material(s)

A two tiered reference standard system was developed consistent with ICHQ6B recommendations. The primary reference standard is not used for routine testing but rather to anchor the potency, purity, and other quality attributes for all future reference standards. The working reference standard is used for routine testing. The primary and working reference standards (b) (4) for pivotal Phase III clinical trials. The reference standards were rigorously characterized by both release testing and additional biochemical characterization. The reference standards are suitable for their intended uses in alirocumab testing. For additional information see Appendix A of the initial integrated review memo.

5. Manufacturing process summary

(b) (4)



(b) (4)

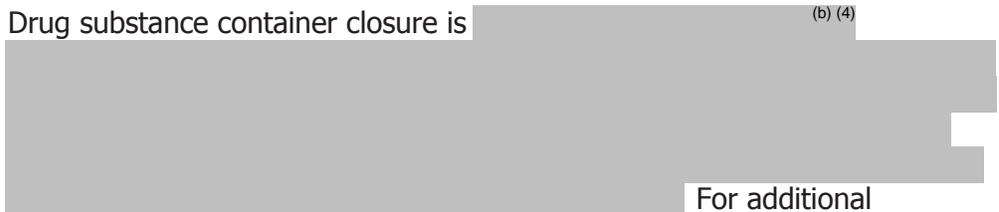


The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with in-process and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents.

For additional information see Appendix A and Appendix B of the initial integrated review memo.

6. Container closure

Drug substance container closure is (b) (4)



For additional information see Appendix A and Appendix B of the initial integrated review memo and [Appendix A](#) of this memo.

7. Dating period and storage conditions: The sponsor conducted real time, accelerated, and stressed stability studies to support their proposed dating period of (b) (4) months when stored at (b) (4) in the dark.

C. Drug Product: Praluent 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. For additional information on the characterization of Praluent see Appendix A for the Drug Substance and Drug Product Quality Technical Report: OBP Assessment and

Appendix C Drug Substance Microbiology Review: Division of Microbiology
Assessment of the initial integrated review memo.

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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety (infection) Efficacy (b) (4)	(b) (4)	(b) (4)	PMCs are in place to confirm that the (b) (4)
Endotoxin	Safety (b) (4)	(b) (4)	(b) (4)	PMCs are in place to confirm that

		(b) (4)	(b) (4)	reduced endotoxin recovery is not observed with the (b) (4)
(b) (4)				
Identity	Safety and Efficacy	N/A	Identity is controlled by PSCK9 specific (b) (4)	
Appearance Physical Form, Clarity,Color	Safety and Efficacy	(b) (4)	(b) (4)	

a. Potency and Strength

Potency is defined as the percent activity relative to alirocumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Praluent will be available in two strengths: 75 mg/ml or 150mg/ml.

b. Summary of Product Design

Praluent will be available in packs of 1, 2, (b) (4) pre-filled syringes with staked needles or pre-filled pens. The functionality and design of the pre-filled syringes and pens was reviewed by CDRH. The pre-filled syringes are assembled into single use disposable autoinjectors to manufacture pre-filled pens that are designed to deliver the entire content of the syringe. The pre-filled syringes and pens were reviewed by CDRH for functionality. CDRH recommends approval of the syringes and pens.

c. Excipients

(b) (4) Histidine, (b) (4) Polysorbate 20 and Sucrose. The excipients used in manufacturing are acceptable because they are compendial quality standards. The excipients are safe for use since they are not of human or animal origin and therefore are of little risk for viral or TSE contamination. For additional information see Appendix A of the initial integrated review memo.

d. Reference material(s)

There is no drug product specific reference material. The primary and working reference materials are drug substance. Please see drug substance reference materials for information.

e. Manufacturing Process

(b) (4)

(b) (4)

Therefore, six PMCs are included with the approval of this application. For further information see Appendix C of the initial review memo and [Appendix B](#) of this memo.

f. Container Closure System

The primary container closure system for Praluent solution for injection is a single-use 1 mL clear glass syringe barrel equipped with a 27G (b) (4)

(b) (4) stainless steel staked needle and a (b) (4) rubber plunger stopper. The drug product CCS is suitable because the components are suitable for parenteral products with minimal leaching and with minimal degradation during the dating period when stored in the dark.

g. Expiration Date & Storage Conditions

The sponsor conducted real time, accelerated, and stressed stability studies on bulk pre-filled syringes, pre-filled syringes and pre-filled pens to support a dating period of 18 months when stored at 2-8°C when stored in the dark. For further information see Appendix A of the initial integrated review memo and [Appendix A](#) of this memo.

h. List of co-packaged components N/A

D. Novel Approaches/Precedents N/A

E. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C

Do not freeze

Do not expose to extreme heat

Protect from light

Time out of refrigeration should not exceed 24h.

F. Establishment Information

OVERALL RECOMMENDATION: Approval					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
			(b) (4) PLI Inspection Requested	3 Item 483	Approved based on the facility profile with an inspection re-evaluation date of (b) (4) .
			Inspection deferred based on Facility profile	N/A	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)
			No inspectional history, DO Inspeccion Requested	N/A	Facility withdrawn by the applicant. The facility has no inspectional history.
			No inspectional history, DO Inspeccion Requested	N/A	Facility withdrawn by the applicant. The facility has no inspectional history.
			Inspection deferred based on Facility profile	N/A	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)

(b) (4)					
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER		INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
(b) (4)	(b) (4)	(b) (4)	Inspection Waived	N/A	Inspection Waived, An inspection is not required to approve BLA 125559.
(b) (4)	Sanofi Winthrop Industrie 1051 Boulevard Industriel 76580 LeTrait, France	3003259844	PLI Inspection Requested	2 Item 483	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)
(b) (4)	Sanofi Chimie 9 quai Jules Guesdes 94400 Vitry sur Seine, France	3002808000	Inspection deferred based on Facility profile	N/A	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)

(b) (4)					
(b) (4)	Sanofi-Aventis Deutschland GmbH Brüningstraße 50 Industriepark Höchst 65926 Frankfurt am Main Germany	3003195501	CDRH/OC Facility Review Requested	N/A	An inspection is not required to approve BLA 125559 as the previous 2013 inspection covered applicable QSRs under 21 CFR 820 and was classified VAI. See CDRH/OC review memo for (b) (4). The inspection re-evaluation date is (b) (4)
		(b) (4)	PLI Inspection Requested	3 Item 483	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)
	Sanofi-Aventis U.S. LLC 6239-6244 Lemay Ferry Road Saint Louis, MO 63129	1000117606	Inspection Waived	N/A	Inspection Waived, the facility is currently in compliance through and is found to be acceptable.

G. Facilities

The subject BLA proposes manufacture of Alirocumab Drug Substance and Drug Product at the following facilities.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

For a complete summary see Appendix D: Drug Substance Facilities Review: Division of Inspectional Assessment of the initial review and [Appendix C](#) of this addendum.

H. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved: annual stability protocol, stability protocol for the extension of shelf-life, and qualification of new working reference standard.
- ii. Outstanding review issues/residual risk - none
- iii. Future inspection points to consider - none

b. Drug Product

- i. Protocols approved: annual stability protocol, stability protocol for the extension of shelf-life.

- ii. Outstanding review issues/residual risk – see sections 1A and 1B of this memo for post-marketing commitments.
- iii. Future inspection points to consider – see addendum to this memo.

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 _____			
Quality Considerations				
21.	Drug Substance Overage		X	

22.	Design Space	Formulation	(b) (4)		
23.		Process			
24.		Analytical Methods			
25.		Other			
26.	Other QbD Elements			X	
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 _____				

3 pages of Appendix A have been withheld in full immediately following this page as a duplicate copy of the "Product Quality Amendment" dated 7/14/2015 which can be found in this review.



The following 34 pages of Appendix B consist of a Product Microbiology review which has been withheld in full from this Product Quality review. The entire Microbiology review dated 07/24/15, can be found in the Microbiology/Virology review section of this approval package.



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: July 16, 2015

To: Administrative File, STN 125559/0

From: Michael R. Shanks, Reviewer, CDER/OPQ/OPF/DIA

Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA

Subject: **ADDENDUM** New Biologic License Application (BLA) Appendix C

US License: 1752

Applicant: Sanofi-Aventis U.S. LLC

Mfg Facility: Drug Substance: [REDACTED] (b) (4)

Drug Product: Sanofi Winthrop Industrie, LeTrait, France (FEI 3003259844)

Product: Praluent[®] (alirocumab, SAR236553, REGN727)

Dosage: Sterile solution supplied in the following presentations for injection, in a pre-filled syringe, 75 and 150 mg/mL, and a pre-filled pen, 75 and 150 mg/mL.

Indication: Treatment for the indications of (1) hyperlipidemia and mixed dyslipidemia.

Due Date: July 24, 2015

Recommendation: The submission is recommended for approval from a facility review perspective.

2 pages of Appendix C have been withheld in full immediately following this page as a duplicate copy of the "Product Quality Amendment" dated 7/20/2015 which can be found in this review.



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

Date: July 16, 2015
To: Administrative File, STN 125559/0
From: Michael R. Shanks, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: ADDENDUM New Biologic License Application (BLA)
US License: 1752
Applicant: Sanofi-Aventis U.S. LLC
Mfg Facility: Drug Substance: (b) (4)
Drug Product: Sanofi Winthrop Industrie, LeTrait, France (FEI 3003259844)
Product: Praluent® (alirocumab, SAR236553, REGN727)
Dosage: Sterile solution supplied in the following presentations for injection, in a pre-filled syringe, 75 and 150 mg/mL, and a pre-filled pen, 75 and 150 mg/mL.
Indication: Treatment for the indications of (1) hyperlipidemia and mixed dyslipidemia.
Due Date: July 24, 2015

Recommendation: The submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Alirocumab Drug Substance and Drug Product at the following facilities.

(b) (4)
A three item 483 was issued with a final recommendation of VAI.

(b) (4)
is performed at Sanofi Winthrop Industrie, LeTrait, France (FEI #2977302488). A PLI was conducted on April 7-14, 2015. A two item 483 was issued with a final recommendation of VAI.

(b) (4)

is performed at Sanofi-Aventis Deutschland GmbH (FEI #3003195501). This facility status is acceptable based on a CDRH recommendation documented in CDRH/OC review memo for ICC 1400731. The previous inspection conducted in 2013 covered applicable QSRs under 21 CFR 820, and was classified VAI. A pre-approval inspection is not required to support this BLA.

Sanofi-Aventis U.S. LLC (1000117606) performs (b) (4). All other facilities performing testing on DS and DP are acceptable or pending compliance review. The facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of Alirocumab Drug Substance and Drug Product.

ASSESSMENT

DRUG SUBSTANCE

3.2.S.2.1 Manufacturers

Current PAI Outcome

(b) (4) with a three item 483 was issued during the PLI with a final recommendation of VAI. The inspection re-evaluation date is (b) (4).

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

(b) (4) has no inspectional history. *The Facility was withdrawn by the Sponsor.*

(b) (4) has no inspectional history. *The Facility was withdrawn by the Sponsor.*

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

Review comment: The compliance status of the facilities associated with the manufacture of alirocumab drug substance is acceptable.

—Satisfactory—

DRUG PRODUCT

3.2.P.2.1 Manufacturers

Current PAI Outcome

Sanofi Winthrop Industrie's (FEI 3003259844) was inspected on 4/06-10/2015 with a two item 483 was issued during the PLI with a final recommendation of VAI. The inspection re-evaluation date is (b) (4).

Sanofi Chimie's (FEI 3002808000) was approved based on the facility profile with an inspection re-evaluation date of (b) (4)

Sanofi-Aventis Deutschland GmbH's (FEI 3003195501) was approved on a CDRH recommendation based on CDRH/OC review memo for ICC 1400731. An inspection is not required to approve BLA 125559 as the previous 2013 inspection covered applicable QSRs under 21 CFR 820 and was classified VAI. The inspection re-evaluation date is (b) (4).

(b) (4) with a three item 483 was issued during the PLI with a final recommendation of VAI. The inspection re-evaluation date is (b) (4)

Sanofi-Aventis U.S. LLC's (FEI 1000117606) (b) (4) the facility is currently in compliance through 2/12/2018 and is found to be acceptable.

Review comment: The compliance status of the facilities associated with the manufacture of alirocumab drug product is acceptable.

—Satisfactory—



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892
Tel. 301-827-1790

Memorandum of Review

STN: BLA125559

Subject: Product Quality Amendment to OPQ Original BLA125559

Date: 5/28/2015

Review/Revision Date:

Primary Reviewer: Richard Ledwidge, PhD

Richard
Ledwidge -S

Digital signed by Richard Ledwidge S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
o=92342.19200300.100.1.1=0012369707
cn=Richard Ledwidge S
Date: 2015.07.14.12.11.58.04.00

Secondary Reviewer: Howard Anderson, PhD

Howard A.
Anderson -A

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05528, cn=Howard A. Anderson A
Date: 2015.07.14.13.53.30.04.00

BACKGROUND

As per CDER 21st Century Review Guidelines, the product quality review for BLA125559 were completed and submitted into Panorama on April 24, 2015. However, at that time there were four outstanding issues that were yet to be resolved because information requests were submitted to the sponsor late in the review cycle. This amendment provides an evaluation of all outstanding review issues.

The review is organized as follows:

- In **Bold font** is the FDA information request.
- In normal font is a summary of the sponsor's response.
- In *italic font* is the reviewer's evaluation of the sponsor's response.

In summary, all product quality issues associated with this BLA are resolved.

FDA IR April 15, 2015

1) You requested a ^(b)₍₄₎ month dating period for drug product stored at 2-8 °C. ^(b)₍₄₎ you provided ^(b)₍₄₎ 18 months real time stability in bulk pre-filled syringes and 12-14 months real time stability in the final container closure system with Alirocumab that was manufactured by the proposed commercial process. ICHQ5C recommends that expiration dating be based on real time/real temperature results. Provide real time results to support the ^(b)₍₄₎ month dating period.

Sponsor response: In addition to the data submitted in the BLA they provided additional stability data:

- ^(b)₍₄₎ months of real time/real temperature data from 2 supporting stability lots of 75 mg/mL alirocumab in bulk PFS

- 2) (b) (4) months of real time/real temperature data from 1 supporting stability lot of 150 mg/mL alirocumab in bulk PFS
- 3) (b) (4) months of real time/real temperature data from 2 supporting lots of 150 mg/mL alirocumab in PFP with (b) (4) Performance data are available for one of these lots.

Reviewer's response: The provided real time stability data in the response suggests that the product is stable out to (b) (4) months at both 75 and 150 mg/ml however the lots were manufactured at pilot scale. There is not enough information (i.e. comparability data) to assess how representative the pilot scale process is of the commercial process therefore we can't use the pilot scale data to establish the dating period.

In the IR response the sponsor provided 18 months of real time stability data from the proposed commercial process to support an 18 month expiry.

2) You provided information in the drug substance container closure system leachable study

(b) (4)

Sponsor Response: The sponsor states that the (b) (4) reported in the leachable study (b) (4)

Reviewer Comment: the sponsor provided mass spectrometry data that demonstrates that (b) (4) There is no safety risk to patients. The sponsor's response to the information request is acceptable.

3) In section S.2.3 (Control of Materials) on page 14 you indicate that

(b) (4)

Sponsor's response: The sponsor conducted an (b) (4)

(b) (4)

Reviewer response: The risk assessment contained the following:

(b) (4)

The risk assessment was thorough and scientifically sound. I agree with the sponsor that (b) (4) is very low. The sponsor's response is acceptable.

FDA IR May 8 2015

In BLA125559, amendment 0042 (page 6), it states:

“In addition, release testing does include tests, such as High Molecular Weights, (b) (4) Please refer to P.5.4 Batch analysis – PFP for results of corresponding tests”.

Please indicate the type of (b) (4) (b) (4) in each PFP batch in section P.5.4 of the BLA. This information will allow the agency to assess the impact of a (b) (4) (b) (4) on product quality.

Sponsor's response: Sonofi indicated that, “three 75 mg/ml PFP batches (At the time of BLA submission, three 75 mg/mL PFP batches (lot numbers 8139000001, 8139000002, and 8139000003) had been manufactured with (b) (4) (b) (4). All other 75 mg/mL PFP batches were manufactured with (b) (4) (b) (4).

Reviewer response: The response is adequate. The results in the Batch Analysis section P.5.4 of the BLA indicate that the quality attributes of the product are similar when the product is expelled from PFP using either the (b) (4) (b) (4). There was a concern that the potential increased (b) (4) in the PFP with the (b) (4) (b) (4)s might negatively (e.g. aggregates) impact product quality.

Appendix

Reviewer Comment OBP Systematic Name: In the original quality review for BLA 125559, the OBP systematic name was listed as [REDACTED] (b) (4)

[REDACTED] This chemical name was listed in the eCTD submission under 3.2.S.1.1 (Nomenclature). However, according to Chana Fuchs (OBP Division IV) the OBP systematic name for this product was determined under IND and listed as [REDACTED] (b) (4)

OVERALL REVIEWER CONCLUSIONS:

Overall Reviewer Conclusion: The sponsor's responses to the information request of April 14, 2015 are acceptable. There is no impact on our recommendation for BLA approval.



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

May 1, 2015

To: Julie Goldin, M.D., ODEII, DMEP; Susan Kirshner, Ph.D., Regulatory Branch Chief, DRRB3

From: Amy Rosenberg, M.D., Director, DRRB3

Amy S. Rosenberg -A

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ou=People, 0.9.2342.19200300.100.1.1=1300045963,
cn=Amy S. Rosenberg -A
Date: 2015.07.08 10:14:13 -04'00'

Re: Risk Assessment pertaining to Anti-Drug Antibodies (ADA) to Alirocumab, a PCSK9 specific mAb

Preface

Effects of ADA on Efficacy:

Development of ADA can have no effect in situations where they are of low titer and transient. In contrast ADA can inhibit product activity causing loss of efficacy, or, rarely and paradoxically, can enhance product activity by serving as a “chaperone” and prolonging PK and PD. Loss of efficacy due to development of ADA is most often seen in the setting of high and sustained antibody levels, in which case the therapeutic is diverted into FcR bearing cells away from the intended target. Loss of efficacy also occurs in the setting of development of neutralizing antibodies (NABs), those antibodies specific to key functional domains of the therapeutic. For example for enzyme replacement therapies for lysosomal storage diseases, neutralizing antibody may develop to the cellular uptake domain of the enzyme, or to the catalytic domain. As regards neutralizing activity to a mAb therapeutic, it would block the binding of the Fab portion of the molecule to its intended target. Of further interest in the setting of NABS to mAbs, there is the possibility that the NAB carries the “internal image” of the Complementarity Determining Region of the mAb and thus resembles the protein to which the mAb is specific.

Effects of ADA on Safety

ADA may cause adverse events pertaining to hypersensitivity responses, both type 1 and type 3. These are scaled from minor, injection site reactions to anaphylaxis, a clinical diagnosis with several distinct pathophysiologic pathway: IgE mediated, with release of histamines from mast cells and basophils, IgG mediated with complement fixation, or by release of cytokines thru cross linking of cell surface receptors by the therapeutic (eg TeGenero anti-CD28 mAb). In situations in which high levels of a protein therapeutic are administered in the setting of a robust ADA response, type III hypersensitivity responses may develop with immune complex mediated manifestations such as was the case with Factor IX and ERT in Pompe Disease (refs).

ADA in Studies of Alirocumab

I will focus on the phase III studies as these were done with validated immunogenicity assays thus providing interpretable results.

Per our previous communication to the sponsor, we recognize that most of the cases of ADA were transient and/or of low titer, and had no discernible or sustained effect on LDL-C levels. However, in patients with more sustained binding and neutralizing antibody responses, or in ADA of high titer, we observed two patterns. In some patients, the persistence of antibodies appears to diminish efficacy, with increases in LDL back to baseline. The sponsor provided additional information on the free PCSK9 levels and alirocumab levels on some but not all of these patients. Alirocumab levels were particularly problematic as they were obtained spottily and not clearly with regard to timing of dosing. As regards the assays for these parameters, the free PCSK9 was assessed by an ELISA using a mAb to PCSK9 that binds to an epitope of PCSK9 that is distinct from that to which the therapeutic mAb binds and no interference has been noted (Sang Chung, Clinical Pharmacology reviewer). As regards the ADA assay, the presence of alirocumab was not expected to interfere with its detection as an acid dissociation step is implemented. Moreover, the assay has a high tolerance for the presence of the mAb (200ug/ml).

No effect of ADA

The sponsor provided as much follow up data for patients with sustained ADA and NABs as regards LDL-C, PCSK9 and alirocumab levels. No effect on these parameters was found with detection of ADA in 5 patients with low titer NABs: 001110-840-173-010; 011717-826-006-063; 011717276-008-005; 011717-724-003-013; and 011717-840-113-022.

Effect of ADA on Efficacy: Diminished Efficacy

In 8 patients, the presence of higher titer (>1:240, decided upon in IND discussions) or NABs correlated with changes in LDL-C, free PCSK9 and alirocumab levels though the latter was often inconsistent.

Patient 00112-528-202-003: this patient developed NAB at higher titer (1:960) and his/her LDL-C rose to 2X baseline level with the peak response. This elevation in LDL-C was attributable to cessation of treatment with statins and was not due to an anti-idiotypic antibody that resembled PCSK9. Nonetheless, this was transient and the patient's ADA and NAB diminished to negative with cessation of dosing (day 30 last dose, resumption of dosing day ~250). Following resumption of dosing, ADA evaluation was obtained at only one time point (day~360) and was negative.

Patient 011569-643-929-019: this patient developed a NAB response (1:480) with an increase of LDL-C back to baseline values. Baseline LDLC levels were maintained though the ADA response diminished over time suggesting that the lower dose of alirocumab may have been insufficient to sustain a diminished LDLC. This is further supported by the maintenance of baseline levels of PCSK9 and low/undetectable alirocumab levels. No ADA evaluation was made between days ~170 and ~390, with the last evaluation negative.

Patient 011569-840-913-009: patient developed NABs 1:480 at day 90, the last day of dosing. NABs were sustained for 90 days off treatment, followed by loss of NABs and decreased ADA over time off treatment. Development of NABs at day 90 correlated with return of LDLC to baseline and a spike in PCSK9 levels. Alirocumab levels were not evaluated at timepoints between day 0 and last day of dosing.

011717-826-007-200: patient developed NABs at day 90 (?1:120) with a rise in LDLC as well as PCSK9 levels to baseline. Although NABS were diminished, the ADA level was still positive, though less than 1:240) at the last timepoint assessed (~day170). Assessment of PCSK9 and alirocumab levels was not performed at later time points in the face of a sustained low titer response.

012492-376-401-009: patient developed transient high titer NAB response day 90 (1:3840). Coincident was a rise in LDLC to baseline and increase in PCSK9 both of which diminished as the ADA diminished. Alirocumab levels increased accordingly with the diminution of the ADA response in subsequent time point evaluations.

017717-826-007-195: patient had a transient elevation in ADA to 1:240 at day 90 with transient elevation of LDL to baseline and PCSK9. Alirocumab levels were non detectable at both of the time points assessed. No further assessment of PCSK9 or alirocumab were made following diminution of the ADA (and one positive NAB determination) to 1:60 day~370.

011568-840-851-004: patient developed NABs, detected ~D190 with subsequent rise in LDLC to near baseline levels.

011569-348-908-005: patient developed NABs, detected ~D90 with rise in LDLC to greater than baseline values, but unclear if on or off statins at baseline and at follow up times later in the course. Follow up testing on the course of the antibody response and changes in LDLC were lacking.

Patients with ADA with Apparent Enhancing Activity

In two patients, the development of ADA appeared to enhance the efficacy of alirocumab.

001119-376-934-002: patient developed NABs on day 90 (1:240) which boosted on day ~180 (1:480), although last dose appeared to be day ~160. Coincident with development of NABs, the LDLC levels dropped to levels <50mg/dl. Intriguingly, these very low LDLC levels were maintained to at least day 250 although dosing had ceased at day ~160 whereas the starting baseline value in this patient was 200 mg/dl. Unfortunately, no further data on NAB level was obtained beyond day 180 and neither PCSK9 nor alirocumab levels were obtained at any time point for this patient.

011717-100-005-016: patient developed ADA and NABS late in the treatment course (day 360) that were sustained at day 460 with a 1:240 titer. While LDLC levels had gradually crept up to baseline prior to development of NABS, they diminished coincident with development of NABS. Although early data were obtained on PCSK9 and alirocumab levels, no evaluations of these parameters were made at the later time points when the ADA developed. It is unclear if the level of NAB in this patient simply had no effect, or actually enhanced activity of alirocumab.

Suggested PMCs:

- 1) Assessment of development of ADA and NABs at late timepoints. Since this treatment is expected to continue potentially for the life of the patients, it is critical to evaluate the later development of ADA and NABs and to assess the effects on efficacy and safety. Thus a PMC should be crafted to cover such a study. Moreover, the company should commit to assessing ADA and NABs in all patients who lose efficacy to discern whether ADA is responsible versus other causes.
- 2) PMC to assess PCSK9 levels and alirocumab levels in patients with high titer/NAB. These evaluations appeared to be done for some, but not all patients and often only at early time points. A PMC should be crafted for a study to assess effects of development of ADA and NABS on PCSK9 and potentially alirocumab levels
- 3) PMC for development of anti-idiotypic antibodies with PCSK9 activity

Given that patients will be treated for very prolonged time periods, perhaps for a lifetime, the loss of product efficacy due to NABs in which LDLC levels increase to greater than baseline values should prompt evaluation of whether the NABs have PCSK9 activity per bearing the internal image of PCSK9. This could be tested very simply by evaluating the binding of the NABs to LDLR.

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/s/

ANITA N BROWN
07/08/2015

AMY S ROSENBERG
07/08/2015



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

May 1, 2015

To: Mary Roberts, M.D., Medical Officer, ODEII, DMPEP; Susan Kirshner, Ph.D., Regulatory Branch Chief DRRB3, OBP

From: Amy S. Rosenberg, M.D. Director DRRB3, OBP

Amy S.
Rosenberg -A

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ou=FDA, ou=People,
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cn=Amy S. Rosenberg -A
Date: 2015.07.08 16:12:52 -0400

Re: Immunogenicity evaluation (safety) for Alirocumab BLA 125559

Overall, immunogenicity was not a prevalent problem with respect to clinical studies of Alirocumab. Most antibody responses were transient. With regard to hypersensitivity responses, although generalized hypersensitivity responses were infrequent, two patients had treatment discontinued due to such responses. Moreover, injection site reactions were notable and higher in the mAb treated group than in the control, presumably excipient only, treated group.

Injection Site Reactions

The presence of positive ADA was associated with a higher incidence of injection site reactions (10.2% vs 5.9%). 8 mAb treated patients and 6 controls discontinued treatment because of such responses.

Proposed PMC: Sponsor should assess whether injection site reactions could be relieved by co- or pre-treatment with local steroid and/or anti-histamine applications, at least where such responses cause patients to discontinue a highly effective therapy. Patients in the control arm with such reactions could be responding to (b) (4) excipient and this should be evaluated in the PMC as well.

Generalized Hypersensitivity Responses

Among patients exhibiting more generalized hypersensitivity responses, including those who met the criteria for anaphylaxis (1), only two patients had to cease dosing. These two patients had ADA detected on at least one occasion but an isotype analysis was not performed, nor was skin testing, a more sensitive evaluation for IgE. Thus, there should be a PMC for the sponsor to investigate the basis of such generalized hypersensitivity responses: if antibody mediated, whether they are IgG or IgE responses; if not antibody mediated, whether they are triggered by an excipient,

(b) (4)

. If an anaphylactic response is IgE mediated and the product is highly effective and no other therapeutic options are available, one could consider using omalizumab (anti-IgE) so the patient could be safely dosed (see ref to Pompe experience); if IgG mediated, consideration could be given to desensitization or tolerance induction protocols if there are no other effective therapeutic options. If such responses result from a cytokine release syndrome (usually a first dose effect and diagnosed by measurement of inflammatory cytokines in serum following product infusion), consideration could be given to administering anti-IL-6, and anti-TNF (all approved products) prior to dosing. This, however, may prove difficult in the case of a q2week administration schedule. Moreover, this is unlikely with respect to a mAb to a soluble factor, albeit that soluble factor binds to a cell surface receptor which can theoretically be cross linked. However, LDLR is not known to have signaling capacity as regards cytokine release. It should be further noted that many patients had generalized hypersensitivity responses in the absence of ADA. These patients may well be responding to the excipient

(b) (4)

Given this background, the following PMCs are in order:

- 1) Investigation of the immunologic basis for significant hypersensitivity responses, especially ones that meet the criteria for anaphylaxis and preclude further product use. The following assessments that shed light on mechanism will inform mitigation strategies (4):

- a. Skin testing (for IgE) should be performed on product and, if positive, on the API and the excipient separately to distinguish specificity.
 - b. Additional assessments, such as evaluation of serum/urinary histamine, serum tryptase, and complement components, and inflammatory cytokines including TNF- α , INF- γ and IL-6 following development of hypersensitivity responses should be considered.
- 2) PMC for determination of ADA and isotype analysis for all patients who have generalized hypersensitivity responses and are antibody positive. Because different mitigation strategies could come into play depending on isotype, eg, anti-IgE mAb (omalizumab) for IgE mediated responses, desensitization/tolerance induction for IgG responses in patients who lack other therapeutic options.

Delayed (Type III) Hypersensitivity Responses

An additional concern is type 3 hypersensitivity responses which can cause immune complex disease including glomerulopathy, skin disease, fever, myalgias, arthralgias etc. Although these types of responses were not documented as due to ADA in the phase III trial (performed under strict clinical conditions), they could occur in a less stringent clinical setting in which alirocumab is administered in the face of a robust antibody response. Once the product is approved, physicians may be tempted to increase the dose of product should a loss of efficacy be observed that proves attributable to antibody to product. Indeed, this has been observed in the setting of Factor IX deficiency (hemophilia B) and Pompe Disease in which it was hoped that increasing the dose and frequency of administration of product in the face of a robust antibody response, would induce tolerance. Both groups of patients developed an immune complex mediated glomerulopathy (5,6).

PMCs/Labeling to Address Type III hypersensitivity Responses

- 1) As previously suggested for efficacy, all patients who lose efficacy of the product should be evaluated for the basis of such loss. Should it prove to be due to an antibody response, alirocumab should not be administered or the dose increased unless and until the antibody response is diminished or eliminated. Fortunately, for most patients, ADA were transient, but in a less controlled setting, such type III HS responses, though not highly likely, are much more probable than in the clinical trial setting.

References

- 1) Sampson HA et al. 2006. Second symposium on the definition and management of anaphylaxis: summary report second NIAID/Food Allergy and Anaphylaxis symposium. *Ann. Emerg. Med.* 47: 373-80
- 2) Vultaggio, A et al. 2014. Manifestations of antidrug antibodies response: hypersensitivity and infusion reactions. *J. of Interferon and Cytokine Research.* 34:946-952
- 3)  (b) (4)
- 4) Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. August, 2014
- 5) Ewenstein B et al. 1997. Nephrotic syndrome as a complication of immune tolerance in hemophilia B. *Blood.* 89:1115
- 6) Hunley TE et al. 2004. Nephrotic syndrome complicating a-glucosidase replacement therapy for Pompe Disease. *Pediatrics.* 114: e532-535.

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/s/

ANITA N BROWN
07/08/2015

AMY S ROSENBERG
07/08/2015

First Approval for Indication Voucher Expedited

Recommendation: Pending

BLA/NDA 125559 Review 1 April 24, 2015

Drug Name/Dosage Form	Praluent (alirocumab)/pre-filled syringe and pre-filled pen
Strength/Potency	75 mg/ml or 150 mg/ml
Route of Administration	Subcutaneous every 2 weeks
Rx/OTC Dispensed	Rx
Indication	Long term treatment of patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia
Applicant/Sponsor	Regeneron
US agent, if applicable	NA

a. Names

- i. Proprietary Name: Praluent
- ii. Trade Name: Praluent
- iii. Non-Proprietary/USAN: alirocumab
- iv. INN Name: alirocumab
- v. Other: REGN727
- vi. OBP systematic name: (b) (4)

- b. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody

Product Overview

Praluent (alirocumab) is a recombinant fully human monoclonal IgG1 antibody produced in CHO cells. Praluent inhibits binding of Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) to the Low Density Lipoprotein Receptor (LDLR) on the surface of hepatocytes. PCSK9 binding to the LDLR promotes LDLR degradation, whereas inhibition of PCSK9 binding leads to increased amounts of cell surface LDLR. Increased amounts of cell surface LDLR lead to reduced serum levels of LDL and related lipoproteins because LDLR binding and internalization is the main clearance mechanism for these lipoproteins. The IgG1 Fc domain of alirocumab does not have effector function so the

mechanism of action of Praluent is only by blocking PCSK9 binding to the LDLR. Praluent is proposed for the treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-cholesterol (LDL-C), total-C, non-high density lipoprotein (non-HDL) -C, Apolipoprotein B, triglycerides, and lipoprotein(a), and to increase HDL-C, and Apolipoprotein A either in combination with a statin or as a monotherapy.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Richard Ledwidge	Division of Biotechnology Review and Research III
Drug Product	Richard Ledwidge	Division of Biotechnology Review and Research III
Facilities	Michael Shanks	Division of Inspectional Assessment
Microbiology Drug Substance	Reyes Candau-Chacon	Division of Microbiology Assessment
Microbiology Drug Product	Colleen Thomas	Division of Microbiology Assessment
Immunogenicity*	Susan Kirshner	Division of Biotechnology Review and Research III
Immunogenicity*	Amy Rosenberg	Division of Biotechnology Review and Research III
DS and DP Team Lead	Howard Anderson	Division of Biotechnology Review and Research III
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment
Business Regulatory Process Manager	Anita Brown	OPRO
Application Technical Lead	Susan Kirshner	Division of Biotechnology Review and Research III

*The immunogenicity review is filed as a separate memo

Multidisciplinary Review Team

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Cross-disciplinary Team Lead	Mary Roberts	ODEII/DMEP
Medical Officer	James Smith	ODEII/DMEP
Medical Officer	Julie Golden	ODEII/DMEP
Pharm/Tox	Lee Elmore, Stephanie Leuenroth-Quinn	ODE II/DMEP
Clinical Pharmacology	Sang Chung, Jayabharathi Vaidyanathan	DCPII
Statistics	Brad McEvoy, Mark Rothmann	DBVI

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	BRANCH/DIVISION	e-Signature
Drug Substance	Richard Ledwidge	Division of Biotechnology Review and Research III	Richard Ledwidge -S Digitally signed by Richard Ledwidge -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012369707, cn=Richard Ledwidge -S Date: 2015.04.28 13:37:13 -04'00'
Drug Product	Richard Ledwidge	Division of Biotechnology Review and Research III	Richard Ledwidge -S Digitally signed by Richard Ledwidge -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012369707, cn=Richard Ledwidge -S Date: 2015.04.28 13:37:44 -04'00'
Facilities	Michael Shanks	Division of Inspectional Assessment	Michael R. Shanks -S Digitally signed by Michael R. Shanks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001408317, cn=Michael R. Shanks -S Date: 2015.04.28 11:31:07 -04'00'
Microbiology Drug Substance	Reyes Candau-Chacon	Division of Microbiology Assessment	Maria D. Candauchacon -S Digitally signed by Maria D. Candauchacon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S Date: 2015.04.28 13:40:28 -04'00'
Microbiology Drug Product	Colleen Thomas	Division of Microbiology Assessment	Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334597 Date: 2015.04.28 11:25:01 -04'00'
DS and DP Team Lead	Howard Anderson	Division of Biotechnology Review and Research III	Howard A. Anderson -A Digitally signed by Howard A. Anderson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605528, cn=Howard A. Anderson -A Date: 2015.04.28 13:46:50 -04'00'
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	Zhihao Qiu -A Digitally signed by Zhihao Qiu -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -A, 0.9.2342.19200300.100.1.1=2000438274 Date: 2015.04.28 15:11:31 -04'00'
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroost -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroost -S Date: 2015.04.30 06:58:46 -04'00'
Application Technical Lead	Susan Kirshner	Division of Biotechnology Review and Research III	Susan L. Kirshner -S Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300194629, cn=Susan L. Kirshner -S Date: 2015.04.28 11:13:32 -04'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 125559/0000	11/24/14
STN 125559/0006	1/27/15
STN 125559/0008	2/13/15
STN 125559/0022	3/26/15
STN 125559/0025	4/06/15
STN 125559/0033	4/17/15

B. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type V	(b) (4)	(b) (4)	5	Pending		DMF is checked out by another reviewer
	Type III		3	N/A			
	Type V		5	Pending		DMF is checked out by another reviewer	
	Type III		5	Pending		DMF is checked out by another reviewer	

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 enough data in the application, therefore the DMF did not need to be reviewed)

C. Other Documents: None

3. CONSULTS: None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

A final recommendation from the Office of Pharmaceutical Quality, CDER, for STN 125559 Praluent (alirocumab) manufactured by (b) (4) is pending due to outstanding requests for information regarding microbiological control and the compliance status of manufacturing sites. There are no outstanding issues for other OPQ product quality disciplines. A final recommendation will be provided in an addendum to this review memo.

a. Benefit/Risk Considerations

Because a final recommendation is not yet available only a preliminary benefit/risk assessment is provided at this time. Praluent is proposed for the treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-cholesterol (LDL-C), total-C, non-high density lipoprotein (non-HDL) -C, Apolipoprotein B, triglycerides, and lipoprotein(a), and to increase HDL-C, and Apolipoprotein A either in combination with a statin or as a monotherapy. High LDL-C is associated with increased risk for serious cardiovascular events, and other cholesterol lowering drugs such as statins are indicated for reducing the risk of serious cardiovascular events in some patients. Praluent was found to be effective in reducing LDL-C to very low levels (b) (4) in subjects who were concomitantly taking statins (b) (4). Therefore, Praluent may address currently unmet medical needs.

The DS manufacturing process is well controlled and should consistently deliver DS of desired quality. No DS related PMCs are requested. However, the compliance status of several DS manufacturing sites is still pending. These facilities include the site for DS manufacture, and in-process and final DS release and stability testing, and two sites for Working Cell Bank release testing.

The review of the microbiological control for the DP manufacturing process is currently incomplete because we are waiting for the applicant to respond to information requests. Otherwise, the DP manufacturing process is well controlled and should consistently deliver DP of desired quality. If this application is approved in this cycle then there will be a need for several product quality microbiology PMCs. The DP quality microbiology PMCs identified thus far are confirmatory studies. (1) The microbial retention study (b) (4)

(2) The bioburden and sterility test methods were qualified with two lots of product. Bacteriostasis/fungistasis was not observed. Method qualification with three different lots of product is required for BLA products due to product complexity. However, because this manufacturing process appears to consistently yield comparable product, comparable method qualification results are expected for the third lot of product.

In addition, the compliance status of several DP manufacturing facilities is pending. These facilities include the site for manufacturing of bulk pre-filled syringes, analytical testing of bulk pre-filled syringes and release testing of pre-filled pens, and the site for stability testing of bulk pre-filled syringe and of pre-filled pen, analytical testing of bulk pre-filled syringe as intermediate and for release testing of the pre-filled pen, Analytical testing of pre-filled pen.

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

Below are draft PMCs to be negotiated with the applicant once the decision to approve has been made.

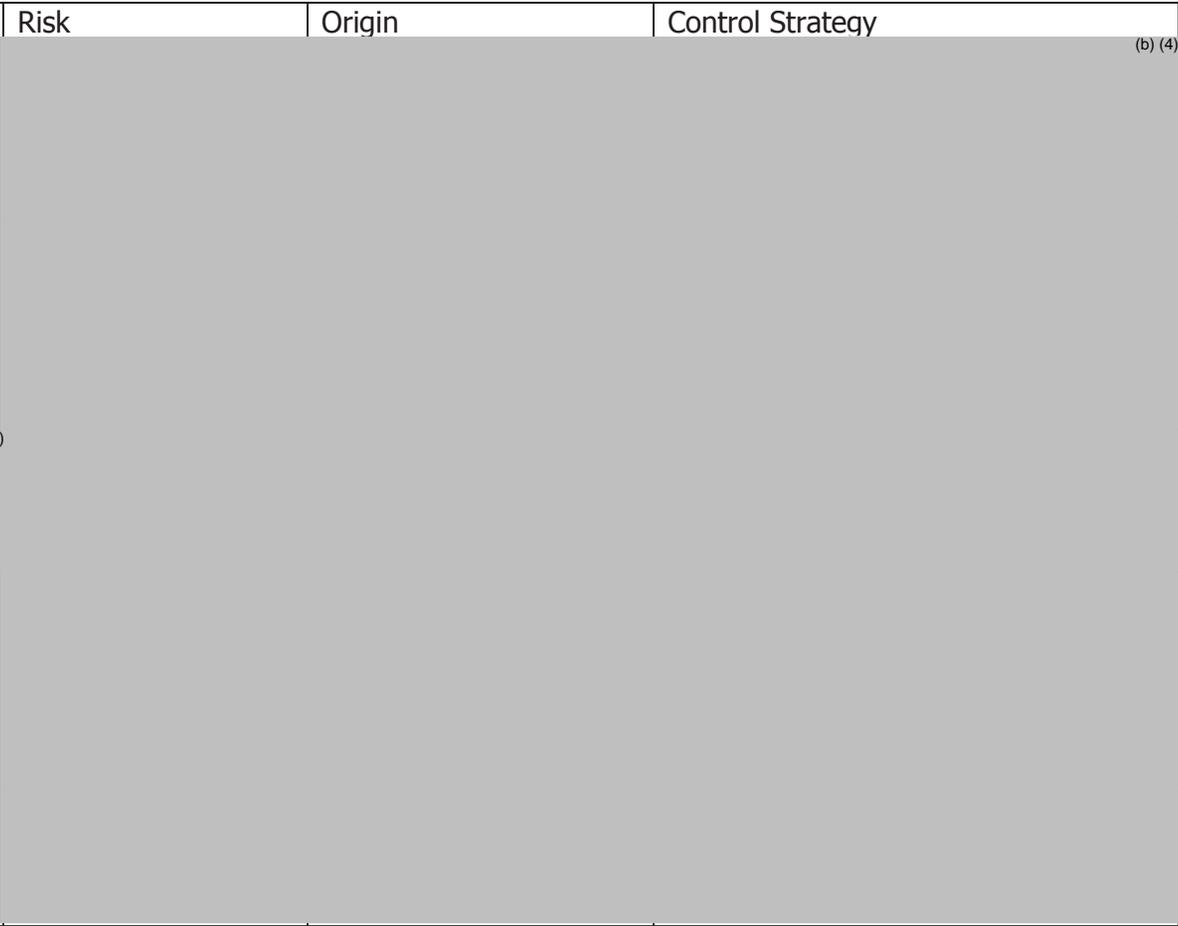
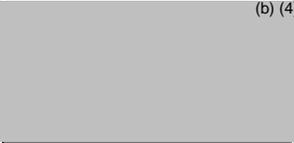
1. To confirm that the [REDACTED] (b) (4)
[REDACTED]
2. Qualification of the bioburden and sterility test methods was performed with only two lots of drug product, with the exception of qualification of the sterility test method for the recovery of *A. brasiliensis*. As a post-marketing commitment, please provide bioburden and sterility test qualification data from one additional batch of 150 mg/ml drug product that was not manufactured from drug substance batches 8065000001 or 8065000002. The study may be done with bulk drug product. The data should be provided in the first annual report.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see [Appendix A](#) for the Drug Substance and Drug Product Quality Review: OBP Assessment.

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

CQA	Risk	Origin	Control Strategy	Other
Potency				(b) (4)
Low Molecular Weight (LMW) Impurities				
				
High Molecular Weight (HMW) Impurities				
Charge Variants				

Appendix A: Drug Substance and Drug Product Quality Review: OBP

B. Drug Substance: Alirocumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see [Appendix A](#) for the Drug Substance and Drug Product Quality Review: OBP Assessment and [Appendix B](#) Drug Substance Microbiology Review: Division of Microbiology Assessment.

Appendix A: Drug Substance and Drug Product Quality Review: OBP

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

CQA	Risk	Origin	Control Strategy	Other
<p>(b) (4)</p>	<p>(b) (4)</p>	<p>(b) (4)</p>	<p>(b) (4)</p>	
	<p>Patient safety</p>			
	<p>Safety and immunogenicity</p>			
	<p>Safety</p>			

Appendix A: Drug Substance and Drug Product Quality Review: OBP

			(b) (4)	
pH	Safety and Efficacy	Formulation		
(b) (4)	Safety and Immunogenicity	(b) (4)		
	Safety			
	Efficacy			
Appearance	Safety and Efficacy			

Appendix A: Drug Substance and Drug Product Quality Review: OBP

Physical Form, Clarity, Color		(b) (4)	(b) (4)
Identity	Safety and Efficacy	N/A	
Osmolality	Safety	Drug product formulation	
Polysorbate 20	Safety	Formulation	
Leachables	Safety	(b) (4)	

Appendix A: Drug Substance and Drug Product Quality Review: OBP

1. Description

Alirocumab is a fully humanized antibody that was generated by standard monoclonal antibody techniques and is expressed in Chinese Hamster Ovary (CHO) cells. (b) (4)

[Redacted text block]

For additional information see [Appendix A](#) and [Appendix C](#).

2. Mechanism of action

Soluble PCSK9 binds a low-density lipoprotein receptor (LDLR) and low-density lipoprotein complex. After internalization the ternary complex is shuttled to the lysosomal compartment for degradation. PCSK9-mediated LDLR degradation causes reduction of LDL-R levels and results in decreased LDL removal from the circulation and concomitantly higher serum LDL. Alirocumab binds PCSK9 with high affinity preventing PCSK9 binding to LDL-R. In the absence of PCSK9, the LDLR/ LDL complex dissociates after internalization, with LDL being shuttled to the lysosome while the LDLR is recycled back to the cell membrane. LDLR recycling causes an increase in LDL removal and a lowering of serum LDL and related lipoproteins. For additional information see [Appendix A](#).

3. Potency Assay

Potency is defined as the percent activity relative to alirocumab reference standard. The potency assay is a cell-based assay that measures the uptake of fluorescently labeled LDL into human liver cell line HepG2/REGN727 and provides an indirect measure of alirocumab's ability to inhibit PCSK9-dependent LDLR degradation. The potency assay is suitable since it is highly relevant to the alirocumab mechanism-of-action and has acceptable precision. For additional information see [Appendix A](#).

4. Reference material(s)

A two tiered reference standard system was developed consistent with ICHQ6B recommendations. The primary reference standard is not used for routine testing but rather to anchor the potency, purity, and other quality attributes for all future reference standards. The working reference standard is used for routine testing. The primary and working reference standards were a (b) (4) for pivotal Phase III clinical trials. The reference standards were rigorously characterized by both release testing and additional biochemical characterization. The reference standards are suitable for their intended uses in Alirocumab testing. For additional information see [Appendix A](#).

Appendix A: Drug Substance and Drug Product Quality Review: OBP

5. Manufacturing process summary

(b) (4)



(b) (4)



The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with in-process and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents.

For additional information see [Appendix A](#) and [Appendix B](#).

6. Container closure

Drug substance container closure is a (b) (4)



For additional information see [Appendix A](#) and [Appendix B](#).

7. Dating period and storage conditions: The sponsor conducted real time, accelerated, and stressed stability studies to support their proposed dating period of (b) (4) months when stored at (b) (4) in the dark.

C. Drug Product: Praluent 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. For additional information on the characterization of Praluent see Appendix A for the Drug Substance and Drug Product Quality Technical Report: OBP Assessment and [Appendix C](#) Drug Substance Microbiology Review: Division of Microbiology Assessment.

Appendix A: Drug Substance and Drug Product Quality Review: OBP

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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety (infection) Efficacy (b) (4)	(b) (4)	(b) (4)	PMC requested to confirm that the (b) (4)

Appendix A: Drug Substance and Drug Product Quality Review: OBP

Endotoxin	Safety (b) (4)	[Redacted]	
[Redacted]	(b) (4)		
Identity	Safety and Efficacy		
Appearance Physical Form, Clarity,Color	Safety and Efficacy		

Appendix A: Drug Substance and Drug Product Quality Review: OBP

a. Potency and Strength

Potency is defined as the percent activity relative to alirocumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Praluent will be available in two strengths: 75 mg/ml or 150mg/ml.

b. Summary of Product Design

Praluent will be available in packs of 1, 2, (b) (4) pre-filled syringes with staked needles or pre-filled pens. The functionality and design of the pre-filled syringes and pens was reviewed by CDRH. The pre-filled syringes are assembled into single use disposable autoinjectors to manufacture pre-filled pens that are designed to deliver the entire content of the syringe. The final assessment from CDRH is still pending and will be provided in an addendum to this review.

c. Excipients

(b) (4) Histidine, (b) (4), Polysorbate 20 and Sucrose. The excipients used in manufacturing are acceptable because they are compendial quality standards. The excipients are safe for use since they are not of human or animal origin and therefore are of little risk for viral or TSE contamination. For additional information see [Appendix A](#).

d. Reference material(s)

There is no drug product specific reference material. The primary and working reference materials are drug substance. Please see drug substance reference materials for information.

e. Manufacturing Process

(b) (4)

(b) (4)

(b) (4)

Appendix A: Drug Substance and Drug Product Quality Review: OBP

(b) (4)

additional information see [Appendix C](#).

f. Container Closure System

The primary container closure system for Praluent solution for injection is a single-use 1 mL clear glass syringe barrel equipped with a 27G (b) (4) stainless steel staked needle and a (b) (4) rubber plunger stopper. The drug product CCS is suitable because the components are suitable for parenteral products with minimal leaching and with minimal degradation during the dating period when stored in the dark.

g. Expiration Date & Storage Conditions

The sponsor conducted real time, accelerated, and stressed stability studies on bulk pre-filled syringes, pre-filled syringes and pre-filled pens to support a dating period of 18 months when stored at 2-8°C when stored in the dark.

h. List of co-packaged components N/A

D. Novel Approaches/Precedents N/A**E. Any Special Product Quality Labeling Recommendations**

Store in a refrigerator at 2-8°C

Do not freeze

Do not expose to extreme heat

Protect from light

Time out of refrigeration should not exceed 24h.



Appendix A: Drug Substance and Drug Product Quality Review: OBP

F. Establishment Information

OVERALL RECOMMENDATION: Pending due to outstanding compliance recommendations and inspections					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
		(b) (4)	PLI Inspection Requested	1 Item 483	Pending Compliance Decision
			Inspection deferred based on Facility profile	N/A	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)
			No inspectional history, DO Inspecton Requested	N/A	<i>DO Inspection Pending</i>
			No inspectional history, DO Inspecton Requested	N/A	<i>DO Inspection Pending</i>
			Inspection deferred	N/A	Approved based on the facility profile with an inspection re-



QUALITY REVIEW STN 125559 Praluent (alirocumab)



Appendix A: Drug Substance and Drug Product Quality Review: OBP

DRUG PRODUCT		(b) (4)	based on Facility profile		evaluation date of (b) (4)
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER		INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
		(b) (4)	Inspection Waived	N/A	Inspection Waived, An inspection is not required to approve BLA 125559.
(b) (4)	Sanofi Winthrop Industrie 1051 Boulevard Industriel 76580 LeTrait, France	3003259844	PLI Inspection Requested	2 Item 483	Pending Compliance Decision
	Sanofi Chimie 9 quai Jules Guesdes 94400 Vitry sur Seine,	3002808000	Inspection deferred based on Facility profile	N/A	Approved based on the facility profile with an inspection re-evaluation date of (b) (4)



QUALITY REVIEW STN 125559 Praluent (alirocumab)



Appendix A: Drug Substance and Drug Product Quality Review: OBP

(b) (4)	France				
	Sanofi-Aventis Deutschland GmbH Brüningstraße 50 Industriepark Höchst 65926 Frankfurt am Main Germany	3003195501	CDRH/OC Facility Review Requested	N/A	An inspection is not required to approve BLA 125559 as the previous 2013 inspection covered applicable QSRs under 21 CFR 820 and was classified VAI. The inspection re-evaluation date is (b) (4)
	(b) (4)	(b) (4)	PLI Inspection Requested	1 Item 483	Pending Compliance Decision
	Sanofi-Aventis U.S. LLC	1000117606	Inspection Waived	N/A	Inspection Waived, the facility is currently in compliance



QUALITY REVIEW STN 125559 Praluent (alirocumab)



Appendix A: Drug Substance and Drug Product Quality Review: OBP

(b) (4)				through and is found to be acceptable.
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Appendix A: Drug Substance and Drug Product Quality Review: OBP

G. Facilities

The subject BLA proposes manufacture of Alirocumab Drug Substance and Drug Product at the following facilities.



(b) (4)

For a complete summary see [Appendix D](#): Drug Substance Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved: annual stability protocol, stability protocol for the extension of shelf-life, and qualification of new working reference standard.
- ii. Outstanding review issues/residual risk - none
- iii. Future inspection points to consider - none

Appendix A: Drug Substance and Drug Product Quality Review: OBP

b. Drug Product

- i. Protocols approved: annual stability protocol, stability protocol for the extension of shelf-life.
- ii. Outstanding review issues/residual risk – see sections 1A and 1B of this memo for post-marketing commitments.
- iii. Future inspection points to consider – see addendum to this memo.

Appendix A: Drug Substance and Drug Product Quality Review: OBP

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 _____			
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	(b) (4)	
23.		Process		
24.		Analytical Methods		
25.		Other		
26.	Other QbD Elements		X	
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	

Appendix A: Drug Substance and Drug Product Quality Review: OBP

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 _____				



Appendix A: Drug Substance and Drug Product Quality Review: OBP

Appendices

Appendix A: Drug Substance and Drug Product Quality Review: OBP

Drug Substance and Drug Product Quality Review OBP**Primary Reviewer – Richard Ledwidge, PhD, Office of Biotechnology Products****Team Leader – Howard Anderson, PhD, Office of Biotechnology Products****1. INSPECTIONAL ACTIVITIES**

A pre-licensure inspection (PLI) of the drug substance manufacturing facility at (b) (4). The inspection covered the manufacturing operations for Alirocumab drug substance manufacturing under BLA STN 125559/0. The inspection was conducted by DMA reviewer, Maria Candauchacon, ORA Chad Thompson, and OBP quality reviewers Richard Ledwidge and Paul Kirwan in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of Alirocumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A three-item 483 was issued; the 483 issues were related to (b) (4) filtration processes, cleaning validation and high rate of invalid assays. The initial recommendation for of the inspection is voluntary action indicated (VAI).

SUMMARY OF QUALITY ASSESSMENTS**I. Primary Reviewer Summary Recommendation**

The Office of Biotechnology Products recommends approval of STN 125559 for PRALUENT (Alirocumab) manufactured by Sanofi-Aventis U.S. LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of PRALUENT (Alirocumab) 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.

The Office of Biotechnology Products recommends approval of the proposed lot release/stability specifications and stability protocols for Alirocumab drug substance and drug product.

The Office of Biotechnology Products recommends an expiry period of (b) (4) months for Alirocumab drug substance when stored at (b) (4) and an expiry period of 18 months for Alirocumab drug product when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated: None

Appendix A: Drug Substance and Drug Product Quality Review: OBP

III. List Of Post-Marketing Commitments/Requirement : None

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance.

V. Primary Container Labeling Review: The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review of Common Technical Document-Quality Module 3.2: This document contains the review of the information provided on Alirocumab drug substance (Section 3.2.S), drug product (Section 3.2.P), adventitious agents safety evaluation (3.2.A), and batch records (3.2.R).

Alirocumab drug substance is [REDACTED] (b) (4)

[REDACTED] Alirocumab is a fully humanized antibody that was generated by standard monoclonal antibody techniques and expressed in Chinese Hamster Ovary (CHO) cells. [REDACTED] (b) (4)

[REDACTED]

Alirocumab drug product is manufactured at Sanofi Winthrop Industrie in LeTrait France. (b) (4)

[REDACTED]

The primary container closure system for Alirocumab solution for injection is a single-use 1 mL clear glass syringe barrel equipped with a 27G [REDACTED] (b) (4) stainless steel staked needle and a [REDACTED] (b) (4) rubber plunger stopper.

Appendix A: Drug Substance and Drug Product Quality Review: OBP

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The review of immunogenicity assays was performed by Susan Kirshner. The immunogenicity risk assessment was performed by Amy Rosenberg, M.D.

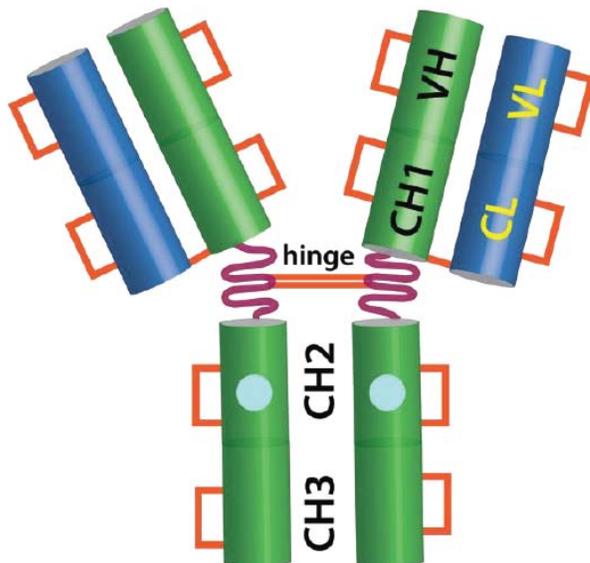
DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

A schematic representation of Alirocumab is shown below:

Figure 2: Schematic Representation of the Structure of Alirocumab



Representation of the structure of alicrocumab depicting the location of each of the intra-chain and inter-chain disulfide bonds (orange). Heavy chains (green) and light chains (blue) are connected by inter-chain disulfide bonds; heavy chain dimerization is achieved through two heavy chain intermolecular disulfide bonds located within the hinge region. The Fc domain glycosylation site is also indicated (cyan).

CH = constant region of the heavy chain; CL = constant region of the light chain; VH = variable region of the heavy chain; VL = variable region of the light chain.

Reviewer Comment: Alirocumab is a fully humanized IgG1 antibody that has a single N-linked glycosylation site (b) (4) in each heavy chain in the constant region (Fc). The heavy and light chains are covalently linked via a disulfide bond. (b) (4)

The Alirocumab primary sequence has a MW of 145, (b) (4) Da (b) (4). The variable regions of the heavy and light chains together form the complementarity-determining regions that bind proprotein convertase subtilisin/kexin type 9 (PCSK9).

3.2.S.1.3 General Properties

The table below is a summary of the biochemical properties of Alirocumab.

QUALITY REVIEW STN 125559 Praluent (alirocumab)

Appendix A: Drug Substance and Drug Product Quality Review: OBP

Table 1: Physicochemical and Biochemical Properties of Alirocumab

Characteristic	Data
Description	Alirocumab is a recombinant human IgG1 isotype monoclonal antibody that specifically binds to proprotein convertase subtilisin kexin type 9 (PCSK9).
Proposed mechanism of action	Soluble PCSK9 binds to (b) (4) low-density lipoprotein receptor (LDLR) and, after internalization, shuttles the receptor to the lysosomal compartment for degradation. A reduction in LDLR expression in the liver, due to PCSK9-mediated LDLR degradation, results in decreased lipoprotein particle removal from the circulation and concomitantly higher serum low-density lipoprotein cholesterol (LDL-C) concentrations. Alirocumab binds PCSK9 with high affinity across multiple species at both neutral and low (endosomal) pH, potently antagonizes PCSK9-mediated effects on LDL uptake (via LDL receptor internalization) by effectively blocking the interaction of PCSK9 with the LDL receptor, and lowers LDL-C in vivo in a dose dependent manner.
Quaternary structure	Covalent heterotetramer consisting of two heavy chains and two light chains
Molecular weight based on primary sequence (b) (4)	145.9 (b) Da (b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Number of disulfide bonds/molecule (b) (4)	(b) (4) disulfide bonds
(b) (4)	(b) (4)
(b) (4)	(b) (4)

Characteristic	Data
(b) (4)	(b) (4)
Appearance of solution	Colorless to pale yellow liquid
Extinction coefficient ^e	(b) (4)
Solubility in Aqueous Solution at Room Temperature	At least 273 mg/mL ^f
(b) (4)	(b) (4)

Appendix A: Drug Substance and Drug Product Quality Review: OBP

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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

Manufacture Process, Controls, Process Development and Process Validation.

1) Manufacturing Facility Information and Manufacturing Process

The drug substance manufacture site information is shown in hyperlink below

[#Manufacturers Table 1](#)

3.2.S.2.2.1 Batch and Scale Definition

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)

BLA STN 125559

Praluent (Alirocumab)

Sanofi-Aventis U.S. LLC

**Drug Substance and Drug Product Reviewer: Richard Ledwidge,
PhD**

**Product Quality Team Leader: Howard Anderson PhD
Review Chief Susan Kirshner PhD**

Office of Biotechnology Products, Division III

**Immunogenicity Reviewer: Amy Rosenberg, M.D. and Susan
Kirshner, PhD.**

OBP CMC Review Data Sheet

1. **BLA#:** 125559
2. **REVIEW DATE:** April 24, 2015
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Mary Roberts, Julie Golden, James Smith
Pharm/Tox: Lee Elmore, Stephanie Leuenroth-Quinn
Product Quality Team: Richard Ledwidge, Howard Anderson, Susan Kirshner
DMA: Maria Candauchacon, Colleen Thomas, Patricia Hughes
Facilities: Michael Shanks, Peter Qiu
Clinical Pharmacology: Sang Chung, Jayabharathi Vaidyanathan
Statistics: Brad McEvoy, Mark Rothmann
OBP Labeling: Jibril Abdus-Samad
RPM: Patricia Madara

4. **MAJOR GRMP DEADLINES**
Filing Meeting: January 7, 2015
Mid-Cycle Meeting: February 25, 2015
Wrap-Up Meeting: June 17, 2015
Primary Review Due: April 24, 2015
Secondary Review Due: May 1, 2015
CDTL Memo Due: June 24, 2015
PDUFA Action Date: July 24, 2015

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information Request 1	January 14, 2015
Filing Meeting	February 15, 2015
Information Request 2	March 10, 2015
Mid Cycle Communication	March 11, 2015
Information Request 3	March 18, 2015
Information Request 4	April 14, 2015

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125559/0000	11/24/14	Yes
STN 125559/0006	1/27/15	Yes
STN 125559/0022	3/26/15	Yes
STN 125559/0025	4/26/15	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: Praluent
- b. Trade Name: Praluent
- c. Non-Proprietary/USAN: Alirocumab
- d. CAS name: 1235916-14-6
- e. Common name: REGN727
- f. INN Name: Alirocumab
- g. Compendial Name: Not applicable
- h. OBP systematic name: (b) (4)
- i. Other Names: REGN727

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant humanized monoclonal antibody

9. **DOSAGE FORM:** solution for injection

10. **STRENGTH/POTENCY:**

Strength: 1 ml of 75 mg/ml or 150 mg/ml in a 1 ml vial.

Potency: Potency is defined as the percent activity relative to Alirocumab reference standard.

The potency assay is a cell-based assay that measures the uptake of fluorescently labeled low-density lipoprotein into human liver cells and provides an indirect measure of Alirocumab to mediate PCSK9-dependent low-density lipoprotein receptor degradation.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)	Provided in the BLA	Type V Sufficient Information was provided in the BLA for its intended use.
			Provided in the BLA	Type III Sufficient Information was provided in the BLA for its intended use.
			Provided in the BLA	Type V Sufficient Information was provided in the BLA for its intended use.
			Provided in the BLA	Type III Sufficient Information was provided in the BLA for its intended use.

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the drug substance manufacturing facility at (b) (4)

The inspection covered the manufacturing operations for Alirocumab drug substance manufacturing under BLA STN 125559/0. The inspection was conducted by DMA reviewer, Maria Candauchaon, ORA Chad Thompson, and OBP quality reviewers Richard Ledwidge and Paul Kirwan in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of Alirocumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A three-item 483 was issued; the 483 issues were related to (b) (4) filtration processes, cleaning validation and high rate of invalid assays. The initial recommendation for of the inspection is voluntary action indicated (VAI).

14. CONSULTS REQUESTED BY OBP: NONE

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

16. PRECEDENTS: NONE

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Howard Anderson, PhD Team Leader Office of Biotechnology Products Division III	 <p>Digitally signed by Howard A. Anderson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605528, cn=Howard A. Anderson -A Date: 2015.04.24 12:52:49 -04'00'</p>

Richard Ledwidge, PhD Primary Reviewer
Office of Biotechnology Products
Division III

Richard
Ledwidge -S

Digitally signed by Richard Ledwidge -
S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=00123697
07, cn=Richard Ledwidge -S
Date: 2015.04.24 12:13:01 -04'00'

B. CC Block

Recipient	Date
Clinical Division BLA RPM Patricia Madara	
Office of Biotechnology Products Division III BLA STN 125559	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of STN 125559 for PRALUENT (Alirocumab) manufactured by Sanofi-Aventis U.S. LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of PRALUENT (Alirocumab) 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.

The Office of Biotechnology Products recommends approval of the proposed lot release/stability specifications and stability protocols for Alirocumab drug substance and drug product.

The Office of Biotechnology Products recommends an expiry period of (b) (4) months for Alirocumab drug substance when stored at (b) (4) and an expiry period of 18 months for Alirocumab drug product when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirement : None

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance.

V. Primary Container Labeling Review: The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review of Common Technical Document-Quality Module 3.2: This document contains the review of the information provided on Alirocumab drug substance (Section 3.2.S), drug product (Section 3.2.P), adventitious agents safety evaluation (3.2.A), and batch records (3.2.R).

Alirocumab drug substance is manufactured (b) (4)

(b) (4) Alirocumab is a fully humanized antibody that was generated by standard monoclonal antibody techniques and expressed in Chinese Hamster Ovary (CHO) cells. (b) (4)

(b) (4)

Alirocumab drug product is manufactured at Sanofi Winthrop Industrie in LeTrait France. The manufacturing process includes (b) (4)

The primary container closure system for Alirocumab solution for injection is a single-use 1 mL clear glass syringe barrel equipped with a 27G (b) (4) stainless steel staked needle and a (b) (4) rubber plunger stopper.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The review of immunogenicity assays was performed by Susan Kirshner. The immunogenicity risk assessment was performed by Amy Rosenberg, M.D.

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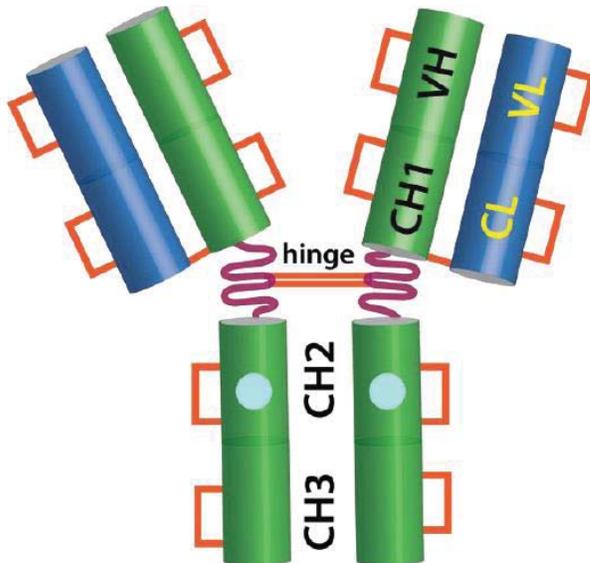
DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

A schematic representation of Alirocumab is shown below:

Figure 2: Schematic Representation of the Structure of Alirocumab



Representation of the structure of alirocumab depicting the location of each of the intra-chain and inter-chain disulfide bonds (orange). Heavy chains (green) and light chains (blue) are connected by inter-chain disulfide bonds; heavy chain dimerization is achieved through two heavy chain intermolecular disulfide bonds located within the hinge region. The Fc domain glycosylation site is also indicated (cyan).

CH = constant region of the heavy chain; CL = constant region of the light chain; VH = variable region of the heavy chain; VL = variable region of the light chain.

Reviewer Comment: Alirocumab is a fully humanized IgG1 antibody that has a single N-linked glycosylation site (b) (4) in each heavy chain in the constant region (Fc). The heavy and light chains are covalently linked via a disulfide bond. (b) (4). The Alirocumab primary sequence has a MW of 145,9 (u) (4) Da (u) (4). The variable regions of the heavy and light chains together form the complementarity-determining regions that bind proprotein convertase subtilisin/kexin type 9 (PCSK9).

3.2.S.1.3 General Properties

The table below is a summary of the biochemical properties of Alirocumab

Table 1: Physicochemical and Biochemical Properties of Alirocumab

Characteristic	Data
Description	Alirocumab is a recombinant human IgG1 isotype monoclonal antibody that specifically binds to proprotein convertase subtilisin kexin type 9 (PCSK9).
Proposed mechanism of action	Soluble PCSK9 binds to the (b) (4) low-density lipoprotein receptor (LDLR) and, after internalization, shuttles the receptor to the lysosomal compartment for degradation. A reduction in LDLR expression in the liver, due to PCSK9-mediated LDLR degradation, results in decreased lipoprotein particle removal from the circulation and concomitantly higher serum low-density lipoprotein cholesterol (LDL-C) concentrations. Alirocumab binds PCSK9 with high affinity across multiple species at both neutral and low (endosomal) pH, potently antagonizes PCSK9-mediated effects on LDL uptake (via LDL receptor internalization) by effectively blocking the interaction of PCSK9 with the LDL receptor, and lowers LDL-C in vivo in a dose dependent manner.
Quaternary structure	Covalent heterotetramer consisting of two heavy chains and two light chains
Molecular weight based on primary sequence (b) (4)	145.9 (b) (4) Da (b) (4)
	(b) (4)
Number of disulfide bonds/molecule	(b) (4) disulfide bonds
	(b) (4)

Characteristic	Data
	(b) (4)
Appearance of solution	Colorless to pale yellow liquid
Extinction coefficient ^e	(b) (4)
Solubility in Aqueous Solution at Room Temperature	At least 273 mg/mL ^f

(b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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

Manufacture Process, Controls, Process Development and Process Validation.

1) Manufacturing Facility Information and Manufacturing Process

The drug substance manufacture site information is shown in hyperlink below

[#Manufacturers Table 1](#)

3.2.S.2.2.1 Batch and Scale Definition

(b) (4)

(b) (4)

180 Page(s) have been
Withheld in Full as b4 (CCI/tS)
immediately following this page



Appendix A: Drug Substance and Drug Product Quality Review: OBP



112 pages of Appendix B and C have been withheld in full immediately following this page as duplicate copies of a Drug Substance Microbiology Review and a Drug Product Microbiology Review. The complete reviews dated 04/24/15 and 04/22/15 can be found in the Microbiology/Virology review section of this approval package.



Facilities Review: Division of Inspectional Assessment

Primary Reviewer: Michael Shanks
Team Lead: Peter Qiu

Recommendation: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Alirocumab Drug Substance and Drug Product at the following facilities.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] A one item 483 was issued with an initial recommendation of VAI. The EIR is now pending compliance review.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED] is performed at Sanofi Winthrop Industrie, LeTrait, France (FEI #2977302488). A PLI was conducted on April 7-14, 2015. A two item 483 was issued with an initial recommendation of VAI, and the EIR is now pending compliance review.

[REDACTED] (b) (4)
[REDACTED] is performed at Sanofi-Aventis Deutschland GmbH (FEI #3003195501). This facility status is acceptable based on a CDRH recommendation documented in CDRH/OC review memo for ICC 1400731. The previous inspection conducted in 2013 covered applicable QSRs under 21 CFR 820, and was classified VAI. A pre-approval inspection is not required to support this BLA.

Sanofi-Aventis U.S. LLC (1000117606) performs [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED], and is found to be acceptable. All other facilities performing testing on DS and DP are acceptable or pending compliance review. The facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of Alirocumab Drug Substance and Drug Product.



Appendix D: Facilities Review: Division of Inspectional Assessment

ASSESSMENT

DRUG SUBSTANCE

3.2.S.2.1 Manufacturers

The proposed alirocumab DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. Alirocumab Drug Substance Facilities.

Site Name	Address	FEI	
(b) (4)			

Review comment: The facilities for the manufacturing, storage, release testing, and stability testing for the alirocumab drug substance are adequately described.

—Satisfactory—



Appendix D: Facilities Review: Division of Inspectional Assessment

Facility Inspection:

Prior Inspection History

(b) (4)
A one item Form FDA 483 was issued. The facility is currently in compliance.

(b) (4)
The facility is currently in compliance.

(b) (4) A GMP inspection is planned for this facility.

(b) (4) A GMP inspection is planned for this facility.

(b) (4)
inspection profile covered CTL. A one item Form FDA 483 was issued. The facility is currently in compliance.

Current PAI Outcome

(b) (4)
A one item Form FDA 483 was issued with an initial recommendation of VAI. *This inspection is still pending a compliance decision.*

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4)

(b) (4) has no inspectional history *and the requested DO inspection is still pending.*

(b) (4) has no inspectional history *and the requested DO inspection is still pending.*

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4)

Review comment: The compliance status of the facilities associated with the manufacture of alirocumab drug substance is adequate.

—Satisfactory—



Appendix D: Facilities Review: Division of Inspectional Assessment

Review comment: [Redacted] (b) (4)

—Satisfactory—

Product Changeover

[Redacted] (b) (4)

—Satisfactory—

DRUG PRODUCT

3.2.P.2.1 Manufacturers

The manufacturing, storage, release testing, and stability testing for the alirocumab drug product are shown in Table 14.

Table 14. Alirocumab Drug Product Facilities.

Site Name	Address	FEI	Responsibilities
[Redacted] (b) (4)			



QUALITY REVIEW STN 125559 Praluent (alirocumab)



Appendix D: Facilities Review: Division of Inspectional Assessment

Sanofi Winthrop Industrie	1051 Boulevard Industriel 76580 LeTrait, France	3003259844	(b) (4)
Sanofi Chimie	9 quai Jules Guesdes 94400 Vitry sur Seine, France	3002808000	
Sanofi-Aventis Deutschland GmbH	Brüningstraße 50 Industriepark Höchst 65926 Frankfurt am Main Germany	3003195501	
Sanofi-Aventis U.S. LLC	6239-6244 Lemay Ferry Road Saint Louis, MO 63129	1000117606	

Review comment: The provided information regarding the identity of the facilities for manufacturing, storage, release testing, and stability testing for alirocumab DP is adequate.

—Satisfactory—



Appendix D: Facilities Review: Division of Inspectional Assessment

Prior Inspection History

The last three inspections of Sanofi Winthrop Industrie (FEI 3003259844) result in VAI and were conducted on (b) (4). Their (b) (4) inspection profile covered (b) (4). A four item Form FDA 483 was issued. The facility is currently in compliance.

The last three inspections of Sanofi Chimie (FEI 3002808000) resulted in VAI and were conducted (b) (4). The (b) (4) inspection profile covered (b) (4). A one item Form FDA 483 was issued. The facility is currently acceptable.

The last three inspections of Sanofi-Aventis Deutschland GmbH (FEI 3003195501) resulted in VAI and were conducted (b) (4). The (b) (4) inspection covered (b) (4). The facility is currently in compliance.

The last three inspections of (b) (4). (b) (4). A one item Form FDA 483 was issued. The facility is currently in compliance.

The last three inspections of Sanofi-Aventis U.S. LLC (FEI 1000117606) resulted in NAI and were conducted (b) (4). The (b) (4) inspection covered (b) (4). The facility is currently in compliance.

Current PAI Outcome

Sanofi Winthrop Industrie's (FEI 3003259844) was inspected on 4/06-10/2015 with a two item 483 was issued during the PLI with an initial recommendation of VAI. *This inspection is still pending a compliance decision.*

Sanofi Chimie's (FEI 3002808000) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

Sanofi-Aventis Deutschland GmbH's (FEI 3003195501) was approved on a CDRH recommendation based on CDRH/OC review memo for ICC 1400731. An inspection is not required to approve BLA 125559 as the previous 2013 inspection covered applicable QSRs under 21 CFR 820 and was classified VAI. The inspection re-evaluation date is (b) (4).

(b) (4) was inspected on (b) (4) under FACTS assignment (b) (4) with a recommendation of VAI. *This inspection is still pending a compliance decision.*

Sanofi-Aventis U.S. LLC's (FEI 1000117606) (b) (4), the facility is currently in compliance through (b) (4) and is found to be acceptable.



Appendix D: Facilities Review: Division of Inspectional Assessment

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

Sanofi-Aventis Deutschland GmbH [REDACTED] (b) (4)

There are no highly toxic, hazardous, or sensitizing materials handled in the areas concerned by alirocumab.

Review comment: The [REDACTED] (b) (4) procedures for alirocumab drug product should be further reviewed during the inspection of the relevant drug product facilities.

Conclusion:

The BLA/Supplement was reviewed from a facility perspective and is recommended for approval.

- 2) (b) (4) months of real time/real temperature data from 1 supporting stability lot of 150 mg/mL alirocumab in bulk PFS
- 3) (b) (4) months of real time/real temperature data from 2 supporting lots of 150 mg/mL alirocumab in PFP with (b) (4). Performance data are available for one of these lots.

Reviewer's response: The provided real time stability data in the response suggests that the product is stable out to (b) (4) months at both 75 and 150 mg/ml however the lots were manufactured at pilot scale. There is not enough information (i.e. comparability data) to assess how representative the pilot scale process is of the commercial process therefore we can't use the pilot scale data to establish the dating period.

In the IR response the sponsor provided 18 months of real time stability data from the proposed commercial process to support an 18 month expiry.

2) You provided information in the drug substance container closure system

(b) (4)
[Redacted]

Sponsor Response: The sponsor states that the (b) (4) reported in the leachable study (b) (4)

*Reviewer Comment: the sponsor provided mass spectrometry data that demonstrates that (b) (4)
[Redacted]
[Redacted] There is no safety risk to patients. The sponsor's response to the information request is acceptable.*

3) In section S.2.3 (Control of Materials) on page 14 you indicate that (b) (4)

[Redacted]

Sponsor's response: The sponsor conducted an (b) (4)

[Redacted]

Reviewer response: The risk assessment contained the following:

(b) (4)

The risk assessment was thorough and scientifically sound. I agree with the sponsor that the risk of adventitious agent contamination from use of (b) (4) development is very low. The sponsor's response is acceptable.

FDA IR May 8 2015

In BLA125559, amendment 0042 (page 6), it states:

"In addition, release testing does include tests, such as High Molecular Weights, (b) (4)

(b) (4)

Please refer to P.5.4 Batch analysis – PFP for results of corresponding tests".

Please indicate the type (b) (4) (b) (4) in each PFP batch in section P.5.4 of the BLA. This information will allow the agency to assess the impact of a (b) (4) on product quality.

Sponsor's response: Sonofi indicated that, "three 75 mg/ml PFP batches (At the time of BLA submission, three 75 mg/mL PFP batches (lot numbers 8139000001, 8139000002, and 8139000003) had been manufactured with a (b) (4)

(b) (4). All other 75 mg/mL PFP batches were manufactured with a (b) (4) (b) (4) ."

Reviewer response: The response is adequate. The results in the Batch Analysis section P.5.4 of the BLA indicate that the quality attributes of the product are similar when the product is expelled from PFP using either the (b) (4) (b) (4). There was a concern that the potential increased (b) (4) in the PFP with the (b) (4) might negatively (e.g. aggregates) impact product quality.

Appendix

Reviewer Comment OBP Systematic Name: In the original quality review for BLA 125559, the OBP systematic name was listed as [REDACTED] (b) (4)

[REDACTED] This chemical name was listed in the eCTD submission under 3.2.S.1.1 (Nomenclature). However, according to Chana Fuchs (OBP Division IV) the OBP systematic name for this product was determined under IND and listed as [REDACTED] (b) (4) [REDACTED] 7.

OVERALL REVIEWER CONCLUSIONS:

Overall Reviewer Conclusion: The sponsor's responses to the information request of April 14, 2015 are acceptable. There is no impact on our recommendation for BLA approval.



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

Date: April 24, 2015
To: Administrative File, STN 125559/0
From: Michael R. Shanks, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 1752
Applicant: Sanofi-Aventis U.S. LLC
Mfg Facility: Drug Substance: [REDACTED] (b) (4)
[REDACTED]
Drug Product: Sanofi Winthrop Industrie, LeTrait, France (FEI 3003259844)
Product: Praluent® (alirocumab, SAR236553, REGN727)
Dosage: Sterile solution supplied in the following presentations for injection, in a pre-filled syringe, 75 and 150 mg/mL, and a pre-filled pen, 75 and 150 mg/mL.
Indication: Treatment for the indications of (1) hyperlipidemia and mixed dyslipidemia.
Due Date: July 24, 2015

Recommendation: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Alirocumab Drug Substance and Drug Product at the following facilities.

[REDACTED] (b) (4) is responsible for DS manufacturing and in-process, release, and stability testing of the DS. [REDACTED] (b) (4) is also responsible for primary stability testing of the bulk pre-filled syringe and the pre-filled pen, [REDACTED] (b) (4) DP, and for release testing of the pre-filled pen, and analytical testing of pre-filled pen. A PLI was conducted on [REDACTED] (b) (4). A one item 483 was issued with an initial recommendation of VAI. The EIR is now pending compliance review.

The manufacturing of [REDACTED] (b) (4)
[REDACTED]
Alirocumab (Praluent) DP is performed at Sanofi Winthrop Industrie, LeTrait, France (FEI #2977302488). A PLI was conducted on [REDACTED] (b) (4). A two item 483 was issued with an initial recommendation of VAI, and the EIR is now pending compliance review.

[Redacted]

[Redacted]

[Redacted]

b(4)

—Satisfactory—

DRUG PRODUCT

3.2.P.2.1 Manufacturers

The manufacturing, storage, release testing, and stability testing for the alicumab drug product are shown in Table 14.

Table 14. Alirocumab Drug Product Facilities.

Site Name	Address	FEI	Responsibilities
[Redacted]	[Redacted]	[Redacted]	[Redacted]
Sanofi Winthrop Industrie	1051 Boulevard Industriel 76580 LeTrait, France	3003259844	[Redacted]
Sanofi Chimie	9 quai Jules Guesdes 94400 Vitry sur Seine, France	3002808000	[Redacted]
Sanofi-Aventis Deutschland GmbH	Brüningstraße 50 Industriepark Höchst 65926 Frankfurt am Main Germany	3003195501	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
Sanofi-Aventis U.S. LLC	6239-6244 Lemay Ferry Road Saint Louis, MO 63129	1000117606	[Redacted]

b(4)

Facility Inspection:

Prior Inspection History

(b) (4)
A one item Form FDA 483 was issued. The facility is currently in compliance.

(b) (4)
The facility is currently in compliance.

(b) (4) has no inspectional history. A GMP inspection is planned for this facility.

(b) (4) has no inspectional history. A GMP inspection is planned for this facility.

(b) (4)
A one item Form FDA 483 was issued. The facility is currently in compliance.

Current PAI Outcome

(b) (4)
A one item Form FDA 483 was issued with an initial recommendation of VAI. *This inspection is still pending a compliance decision.*

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

(b) (4) has no inspectional history *and the requested DO inspection is still pending.*

(b) (4) has no inspectional history *and the requested DO inspection is still pending.*

(b) (4) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

Review comment: The compliance status of the facilities associated with the manufacture of alirocumab drug substance is adequate.

—Satisfactory—

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[REDACTED] is performed at Sanofi-Aventis Deutschland GmbH (FEI #3003195501). This facility status is acceptable based on a CDRH recommendation documented in CDRH/OC review memo for ICC 1400731. The previous inspection conducted in 2013 covered applicable QSRs under 21 CFR 820, and was classified VAI. A pre-approval inspection is not required to support this BLA.

b(4)

Sanofi-Aventis U.S. LLC (1000117606) performs [REDACTED] of the DP, and is found to be acceptable. All other facilities performing testing on DS and DP are acceptable or pending compliance review. The facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of Alirocumab Drug Substance and Drug Product.

b(4)

ASSESSMENT

DRUG SUBSTANCE

3.2.S.2.1 Manufacturers

The proposed alicumab DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. Alirocumab Drug Substance Facilities.

Site Name	Address	FEI	Responsibilities
-----------	---------	-----	------------------

[REDACTED]

[REDACTED]

b(4)

[REDACTED]

[REDACTED]

Review comment: The facilities for the manufacturing, storage, release testing, and stability testing for the alicumab drug substance are adequately described.

—Satisfactory—

Review comment: *The provided information regarding the identity of the facilities for manufacturing, storage, release testing, and stability testing for alirocumab DP is adequate.*

—Satisfactory—

Prior Inspection History

The last three inspections of Sanofi Winthrop Industrie (FEI 3003259844) result in VAI and were conducted on (b) (4). Their (b) (4) inspection profile covered (b) (4). A four item Form FDA 483 was issued. The facility is currently in compliance.

The last three inspections of Sanofi Chimie (FEI 3002808000) resulted in VAI and were conducted (b) (4). The (b) (4) inspection profile covered (b) (4). A one item Form FDA 483 was issued. The facility is currently acceptable.

The last three inspections of Sanofi-Aventis Deutschland GmbH (FEI 3003195501) resulted in VAI and were conducted (b) (4). The (b) (4) inspection covered (b) (4). The facility is currently in compliance.

The last three inspections of (b) (4) were conducted (b) (4). The (b) (4) inspection covered (b) (4). A one item Form FDA 483 was issued. The facility is currently in compliance.

The last three inspections of Sanofi-Aventis U.S. LLC (FEI 1000117606) resulted in NAI and were conducted (b) (4). The (b) (4) inspection covered (b) (4). The facility is currently in compliance.

Current PAI Outcome

Sanofi Winthrop Industrie's (FEI 3003259844) was inspected on 4/06-10/2015 with a two item 483 was issued during the PLI with an initial recommendation of VAI. *This inspection is still pending a compliance decision.*

Sanofi Chimie's (FEI 3002808000) was approved based on the facility profile with an inspection re-evaluation date of (b) (4).

Sanofi-Aventis Deutschland GmbH's (FEI 3003195501) was approved on a CDRH recommendation based on CDRH/OC review memo for ICC 1400731. An inspection is not required to approve BLA 125559 as the previous 2013 inspection covered applicable QSRs under 21 CFR 820 and was classified VAI. The inspection re-evaluation date is (b) (4).

(b) (4) was inspected on (b) (4) under FACTS assignment (b) (4) with a recommendation of VAI. *This inspection is still pending a compliance decision.*

Sanofi-Aventis U.S. LLC's (FEI 1000117606) performs [REDACTED] (b) (4) [REDACTED] the facility is currently in compliance through [REDACTED] (b) (4) and is found to be acceptable.

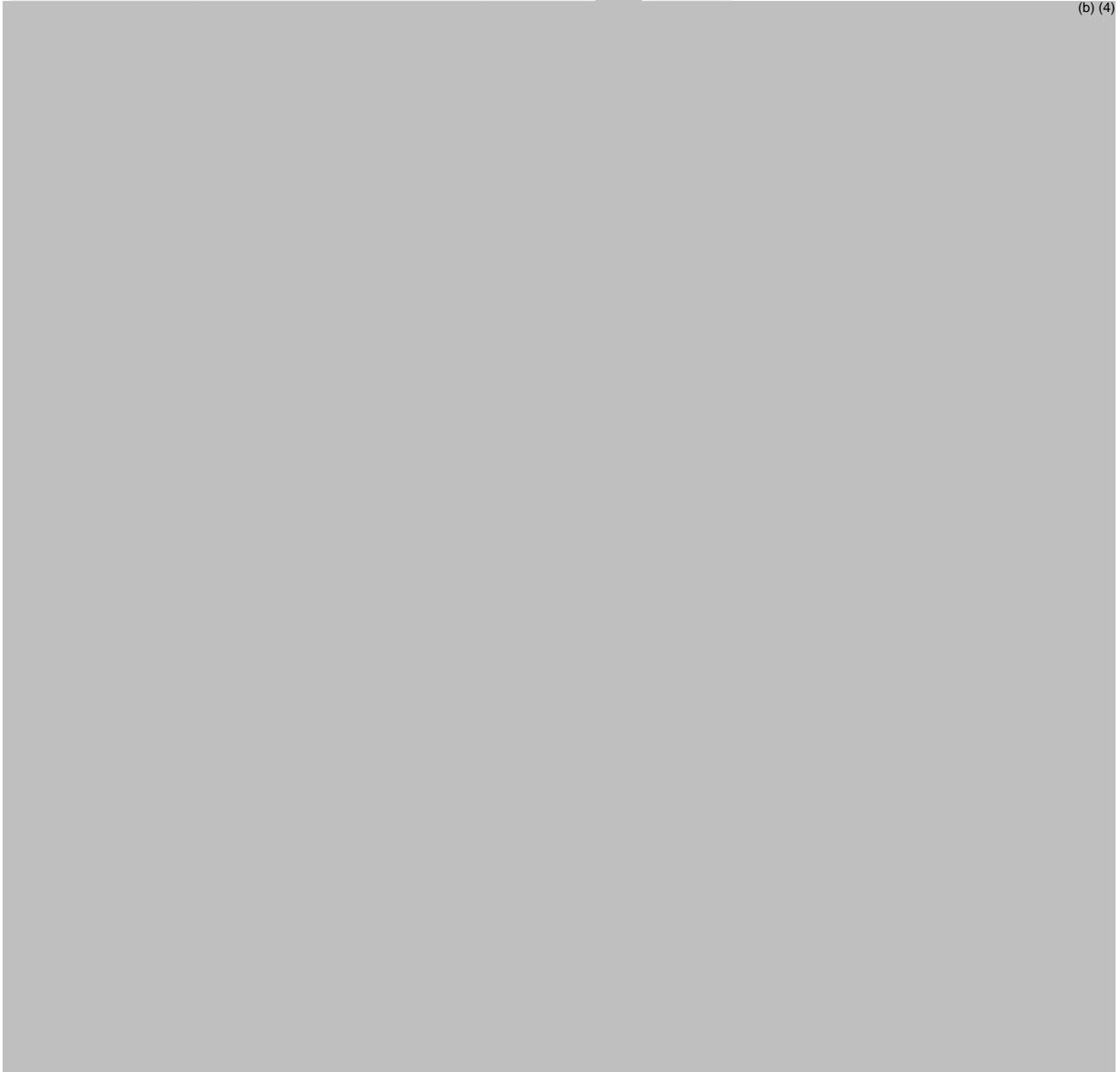
Review comment: The compliance status of the facilities associated with the manufacture of alirocumab drug substance is adequate.

—*Satisfactory*—

3.2.A.1 Facilities and Equipment

Facility Overview

Sanofi Winthrop Industrie Le Trait Drug Product [REDACTED] (b) (4) Facility



(b) (4)



Sanofi-Aventis Deutschland GmbH

(b) (4)

There are no highly toxic, hazardous, or sensitizing materials handled in the areas concerned by alirocumab.

Review comment: The (b) (4) procedures for alirocumab drug product should be further reviewed during the inspection of the relevant drug product facilities.

Conclusion:

The BLA/Supplement was reviewed from a facility perspective and is recommended for approval.

Michael R.
Shanks -S

Digitally signed by Michael R. Shanks -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001408317, cn=Michael R. Shanks -S
Date: 2015.04.24 23:01:43 -04'00'

Zhihao
Qiu -A

Digitally signed by Zhihao Qiu -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -A, 0.9.2342.19200300.100.1.1=2000438274
Date: 2015.04.24 23:24:31 -04'00'

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 125559 Submission Type: BLA

Established/Proper Name:
alirocumab injection

Applicant: Regeneron Letter Date: 11/24/2015

Dosage Form: pre-filled
syringe and pre-filled pen

Chemical Type:
Biologig

Stamp Date: 11/24/2015

Strength: 75 and 150 mcg

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		x	Describe filing issues here or on additional sheets
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		x	Describe potential review issues here or on additional sheets

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	x	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	x	
3.	Naturally-derived Product	<input type="checkbox"/>	x	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	x	
5.	PET Drug	<input type="checkbox"/>	x	
6.	PEPFAR Drug	<input type="checkbox"/>	x	
7.	Sterile Drug Product	x	<input type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	x	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	x	
10.	Locally acting drug ¹	<input type="checkbox"/>	x	
11.	Lyophilized product ¹	<input type="checkbox"/>	x	
12.	First generic ¹	<input type="checkbox"/>	x	
13.	Solid dispersion product ¹	<input type="checkbox"/>	x	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	x	
15.	Modified release product ¹	<input type="checkbox"/>	x	
16.	Liposome product ¹	<input type="checkbox"/>	x	
17.	Biosimilar product ¹	<input type="checkbox"/>	x	
18.	Combination Product	x	<input type="checkbox"/>	Pre-filled syringe and pen
19.	Other	<input type="checkbox"/>	x	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Regulatory Considerations				
20.	USAN Name Assigned	x	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	x	<input type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	x	
24.	Comparability Protocol(s) ²	x	<input type="checkbox"/>	
25.	Other	<input type="checkbox"/>	x	
Quality Considerations				
26.	Drug Substance Overage	x	<input type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	x
28.		Process	<input type="checkbox"/>	x
29.		Analytical Methods	<input type="checkbox"/>	x
30.		Other	<input type="checkbox"/>	x
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	x	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	x	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	x	
34.	Process Analytical Technology ¹	<input type="checkbox"/>	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	x	<input type="checkbox"/>
36.		Excipients	<input type="checkbox"/>	x
37.		Microbial	<input type="checkbox"/>	x
38.	Unique analytical methodology ¹	x	<input type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	x	
40.	Novel Excipients	<input type="checkbox"/>	x	
41.	Nanomaterials ¹	<input type="checkbox"/>	x	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	x	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	x	
44.	Continuous Manufacturing	<input type="checkbox"/>	x	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	x	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	x	
48.	Novel BE study designs	<input type="checkbox"/>	x	
49.	New product design ¹	<input type="checkbox"/>	x	
50.	Other	<input type="checkbox"/>	x	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance	x	<input type="checkbox"/>	<input type="checkbox"/>	

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

C. FILING CONSIDERATIONS				
	<input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 			
FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable) 	x	<input type="checkbox"/>	<input type="checkbox"/>
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle? 	x	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	<input type="checkbox"/>	<input type="checkbox"/>
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture 	x	<input type="checkbox"/>	<input type="checkbox"/>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 			
DRUG PRODUCT INFORMATION				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ☐ Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product 	x	☐	☐

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<p>manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</p> <ul style="list-style-type: none"> ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <ul style="list-style-type: none"> <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <ul style="list-style-type: none"> <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	x	
9.	<p>Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	x	
10.	<p>Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.</p>	<input type="checkbox"/>	<input type="checkbox"/>	x	
11.	<p>For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?</p>	<input type="checkbox"/>	<input type="checkbox"/>	x	
12.	<p>For an extended release dosage form, is there enough information to assess the extended release</p>	<input type="checkbox"/>	<input type="checkbox"/>	x	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	designation claim as per the CFR?			
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	x
REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	x	<input type="checkbox"/>
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	<input type="checkbox"/>	<input type="checkbox"/>
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients 	x	<input type="checkbox"/>	<input type="checkbox"/>
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	x		

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health (CDRH)

Office of Compliance (OC), Division of Manufacturing & Quality (DMQ)

Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch (REGO)

DATE: December 17, 2014

TO: Julie Golden, Medical Office, DMQP, CDER

julie.golden@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Pat Madara

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

Francisco Vicenty -S

2014.12.18 22:53:53 -05'00'

From: Viky Verna, REGO, DMQ, OC, CDRH

Applicant: Sanofi-Aventis LLC

55 Corporate Drive,

Bridgewater, NJ 08807

FEI# 1000117606

Application # BLA 125559

Consult # ICC1400731

Product Name: Praluent

Consult This is a new biologic which has been granted a priority review.

Instructions: There is an 8-month timeline. We would like to request a consult from CDRH/OC to conduct a filing review and determine the need for inspection of device related sites.

Inspection Needed: Yes - Date: 12/17/2014

Documentation Review: No Additional Information Required

Final Recommendation: DELAYED

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Praluent, BLA 125559.

PRODUCT DESCRIPTION

PRALUENT (Alirocumab) is a solution for subcutaneous injection, indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprote in cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1).

PRALUENT is proposed to be available in 75 mg/mL and 150 mg/mL pre-filled pens (PFP) as well as 75 mg/mL and 150 mg/mL pre-filled syringes (PFS). The pre-filled pens and pre-filled syringes are to be packaged in cartons containing one (1), two (2), (b) (4) one mL pre-filled pen(s) or pre-filled syringe(s) for the 75 mg and 150 mg doses.

(b) (4)
(b) (4)
(b) (4) are produced by Sanofi Winthrop Industrie, in Le Trait, France. Sanofi-Aventis Deutschland GmbH, located in Frankfurt, Germany, (b) (4) . Manufacture and supply of the auto-injector sub-assemblies is performed by (b) (4).

Figure 1 - Alirocumab Pre-filled Pens



REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Sanofi Winthrop Industrie
1051 Boulevard Industriel
76580 LeTrait, France
Registration #: 2977302488
FEI #: 3003259844

Responsibility:

(b) (4)

An analysis of the firm's inspection history over the past 2 years showed that the last inspection of the firm performed on (b) (4), covered CDER GMP requirements and was classified as VAI. The previous inspection, (b) (4), covered CBER GMP requirements and was also classified as VAI. An inspection covering applicable Quality System Requirements (QSR, 21 CFR 820) has not been performed within the last two years. Therefore, an inspection covering applicable 21 CFR 820 requirements is recommended for this firm.

2. Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Registration #: 3003195501

Responsibility:

(b) (4)

An analysis of the firm's inspection history over the past 2 years showed that the last inspection of the firm performed on (b) (4), covered CDER GMP requirements and was classified as NAI. The previous inspection, (b) (4), (b) (4), covered GMP and applicable Quality System Requirements (QSR, 21 CFR 820) requirements, and was also classified as VAI. An inspection covering applicable Quality

System Requirements (QSR, 21 CFR 820) performed within the last two years was acceptable. Therefore, an inspection covering applicable 21 CFR 820 requirements is not required for this firm.

DESK REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Sanofi established a Quality Manual which presents current good manufacturing practices (cGMP) requirements applicable to all functions that support clinical and commercial production, storage, testing and distribution. Furthermore, Sanofi has established the quality management system that comprises four elements, as described in their Quality Manual: [REDACTED] (b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm provided information covering the activities performed to confirm the suitability of the device constituent with the drug product for the proposed intended use. [REDACTED] (b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

[REDACTED] (b) (4)

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

MANUFACTURING

Production and Process Controls

Production Flow

A description of the manufacturing process for alirocumab 150 and 75 mg/mL, solution for injection in bulk pre-filled syringe was provided and covered the following steps:

(b) (4)

The firm also described the special controls applied at different stages of the manufacturing process.

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Acceptance Activities

The firm provided the specifications the combination product has to meet throughout the manufacturing process before release.

Test	Analytical Method	Acceptance Criteria
Appearance of Solution a. Physical Form/ Condition b. Clarity	a. Visual inspection b. Visual comparison to reference suspension Ph.Eur. 2.2.1	(b) (4)
Color of Solution	Visual comparison to reference solution Ph. Eur. 2.2.2	(b) (4)
pH	Potentiometer	(b) (4)
Identity by PCSK9-Specific ELISA	ELISA	(b) (4)
Total Protein Content (b) (4)	UV Spectrophotometry	(b) (4)
Potency by Bioassay	Cell-based assay	(b) (4)
Purity by Reduced CE-SDS (b) (4)	Capillary electrophoresis	(b) (4)

Test	Analytical Method	Acceptance Criteria
Purity by Non-Reduced CE-SDS (b) (4)	Capillary electrophoresis	(b) (4)
Purity by Size Exclusion HPLC (b) (4)	Size exclusion high performance liquid chromatography	(b) (4)
		(b) (4)
		(b) (4)
Endotoxin Content	Ph.Eur. 2.6.14/ USP<85> (b) (4)	(b) (4)
Sterility of Pre-filled Syringe	Ph.Eur. 2.6.1/ USP<71> (b) (4)	(b) (4)
Expellable Volume	Weighing of expelled liquid	(b) (4)
Break-Loose Force Glide Force	Force measurement	(b) (4)

Desk Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. Therefore, no additional information is required for the documentation review.

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application BLA 125559 and has the following recommendations:

The approvability of application for Praluent, BLA 125559, should be delayed for the following reasons:

The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. However, a pre-approval inspection is recommended for:

- **Sanofi Winthrop Industrie**
1051 Boulevard Industriel
76580 LeTrait, France
Registration #: 2977302488
FEI #: 3003259844

**Viky
Verna -S**

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Viky Verna -S,
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Viky Verna, MS BME, MS Pharm

Prepared: VVerna: 12/17/2014

Reviewed: FMLast name: Month/Day/Year

Application # BLA 125559

Consult # ICC1400731

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

Inspectional Guidance

CDRH recommends a combination product pre-approval inspection at the following firm:

- **Sanofi Winthrop Industrie**
1051 Boulevard Industriel
76580 LeTrait, France
Registration #: 2977302488
FEI #: 3003259844

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the combination product Praluent, BLA 125559.

Additionally, evaluate the manufacturing activities (b) (4)

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

LT Viky Verna
Compliance Reviewer,
REGO
Division of Manufacturing Quality (DMQ)
Office of Compliance (OC), CDRH
Phone: 301-796-2909

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty
Branch Chief,
REGO
Division of Manufacturing Quality (DMQ)
Office of Compliance (OC), CDRH
Phone: 301-796- 5577

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
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INFORMATION**