PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA: 125559
Applicant: Sanofi-Aventis U.S. LLC
US License Number: 1752
Submission Reviewed: Original BLA
Product: alirocumab (human monoclonal antibody against PCSK9)
Indication: Treatment of hypercholesterolemia and mixed dyslipidemia
Dosage Form: Sterile, preservative-free solution (75 mg/ml and 150 mg/ml) for subcutaneous injection. Supplied in pre-filled syringes and pre-filled pens.
DP Manufacturing Site: Sanofi Winthrop Industrie, Le Trait, France (FEI: 2977302488)
FDA Receipt Date: 24 November 2014
Action Date: 24 July 2015

Conclusion and Approvability Recommendation

The BLA was reviewed for microbial control of the drug product manufacturing process and for drug product sterility assurance. The BLA is recommended for approval from a product quality microbiology perspective. There are six post-marketing commitments, which are listed below.
Drug Product Quality Microbiology PMCs

1. Repeat the microbial retention study 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, 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. Provide the data in the first annual report.

3. Revise the container closure integrity test method to include a system suitability control with Report this change in the first annual report.

4. Implement

5. To confirm that reduced endotoxin recovery over time is not observed with the The study should be designed to support the proposed endotoxin testing

6. Revise the bioburden limit for after data from additional drug product batches has been analyzed.
Product Quality Microbiology Assessment: Drug Product

Reviewer's comment: This review addendum covers drug product quality microbiology information provided in sequences 0022, 0029, 0039, 0042, 0053, and 0058.

Module 3.2.P - Pre-Filled Syringe (PFS)

P.3.3 Description of Manufacturing Process and Process Controls

Reviewer's question: Some of the information provided in section 3.2.P.3.5 and in information request responses should also be provided in section 3.2.P.3 or 3.2.P.5 of the BLA file. Please update the appropriate sections with the following information.

a) Identification of the

b) Description of the

c) The updated

d) The

e) [Redacted] process parameters for equipment and components that contact the referenced in Drug Master Files.

f) We acknowledge the description of the Sanofi endotoxin testing method for the drug product that has already been provided. Although this is a compendial method, the full SOP should still be provided in section 3.2.P.5 as was done for the sterility test method.

The response was provided in sequence 0058. The following information was added to the BLA file:

a) Identification of the

was added to section 4 of module P.3.3.

b) The description of the

was added to section 5 of module P.3.3.

c) The updated

was added to modules P.3.3 and P.3.4.

d) The

was added to module P.3.3.

e) Process parameters for

added to section 6 of module P.3.3. The remainder of the processes are referenced in DMFs.

f) A complete description of the Sanofi endotoxin test method was added to module P.5.2.

SATISFACTORY
PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

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TEAM LEADER: Patricia Hughes, Ph.D.

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Applicant: Sanofi-Aventis U.S. LLC
US License Number: 1752
Submission Reviewed: Original BLA
Product: alirocumab (human monoclonal antibody against PCSK9)
Indication: Treatment of hypercholesterolemia and mixed dyslipidemia
Dosage Form: Sterile, preservative-free solution (75 mg/ml and 150 mg/ml) for subcutaneous injection. Supplied in pre-filled syringes and pre-filled pens.
DP Manufacturing Site: Sanofi Winthrop Industrie, Le Trait, France (FEI: 2977302488)
FDA Receipt Date: 24 November 2014
Action Date: 24 July 2015

Conclusion and Approvability Recommendation

A recommendation cannot be made at this time because additional data is needed in order to complete the product quality microbiology review for the drug product.
Post-Marketing Commitments

1. 

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, 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.

Information Pending

Information on the following topics has been requested, and the response is pending:

- Environmental monitoring
- 
- Sterility testing
- 
- Endotoxin testing

The following topics will be included in future information requests:

- In-process bioburden limit
- Endotoxin monitoring strategy (if applicable)
- Time limit for sterilizing filtration and filling (discussion ongoing)
- PMC for repeat microbial retention study (discussion ongoing)
- Assembly and shipping validation for the PFS and PFP
- Container closure integrity test method for the PFS and PFP

The following DMF reviews are pending. The volumes needed are currently checked out by other reviewers.
Product Quality Microbiology Assessment: Drug Product

Module 3.2.P - Pre-Filled Syringe (PFS)

P.1 Description and Composition of the Drug Product

Alirocumab drug product (DP) is a sterile, preservative-free solution for subcutaneous injection. The DP solution is clear, colorless to pale yellow, and has a pH of 6.0. The DP is supplied in 75 mg/ml and 150 mg/ml strengths. Both DP strengths contain the same formulation components and are supplied in single-use pre-filled syringes (PFS). Both the 75 mg/ml and the 150 mg/ml PFS are filled to ensure a 1.0 ml deliverable volume. The entire contents of the PFS are intended to be injected during administration. The DP composition is described in the table below, which was provided in section P.1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function/Characteristic</th>
<th>Reference to Quality Standard</th>
<th>Concentration</th>
<th>Amount per Pre-filled Syringe (mg)²</th>
<th>Amount per Pre-filled Syringe (mg)²</th>
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<tbody>
<tr>
<td>Alirocumab</td>
<td>active ingredient</td>
<td>in-house specification</td>
<td>75 mg/mL</td>
<td>75.0</td>
<td>150.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USP, Ph. Eur., JP</td>
<td></td>
<td>(b)(4)</td>
<td>(b)(4)</td>
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<td></td>
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<td></td>
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<tr>
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<tr>
<td>Polyborate 20</td>
<td></td>
<td>NF, Ph. Eur., JPE</td>
<td></td>
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</tr>
<tr>
<td>Water for Injection</td>
<td></td>
<td>USP, Ph. Eur.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


DESCRIPTION IS SATISFACTORY

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Conclusion

1. Additional data is needed in order to complete the product quality microbiology review for the drug product. The data has been requested and will be reviewed in an addendum to this memo.

2. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.

3. Inspection follow-up items will be included in the addendum, if applicable.

Product Quality Microbiology PMCs

There will be a PMC for a confirmatory microbial retention study for the sterilizing filter, but the study design depends on the time limit for sterilizing filtration and filling. The sponsor has not yet set a time limit for this unit operation. Refer to the discussion under section P.3.5 for the bulk PFS. The following PMC is a draft which has not yet been sent to the sponsor.

The following PMC has been communicated to the sponsor in an information request:

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, 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.
23 April 2015 (response pending) - IR from CDRH and product quality microbiology

1. Within the original BLA submission, and within your response to several information requests, you have described the following changes to the to-be-marketed PFP versions with respect to the PFP versions for which there is clinical experience:
   a. The to-be-marketed 75mg/ml PFP presentation will have a [REDACTED] while versions of the 75mg/ml PFP used within clinical studies contained a [REDACTED]
   b. The to-be-marketed versions of the 75mg/ml and 150mg/ml PFP will be produced under a process-control method which is intended to ensure that PFSs contained within the PFPs [REDACTED]

Please state how the changes described in a and b, above have been evaluated to ensure that they will not introduce unexpected and undesirable effects on the following [REDACTED]

2. In addition, please clarify whether the [REDACTED]. Describe any additional changes (such as [REDACTED]) that are being considered by the component suppliers to [REDACTED]

Colleen Thomas -S

Patricia F. Hughestroost -S
Date: April 20, 2015
To: Administrative File, STN 125559/0
From: Reyes Candau-Chacon, PhD. Reviewer, DMA/OPF/OPQ
Through: Patricia Hughes, Ph.D., Acting Branch Chief, DMA/OPF/OPQ
Subject: New Biologic License Application (BLA)
US License: 1752
Applicant: Sanofi-Aventis U.S. LLC
Facilities: [redacted]
Product: PRALUENT (alirocumab, SAR236553, REGN727)
Dosage: Sterile solution for subcutaneous injection available in 75 mg/mL and 150 mg/mL prefilled syringes and autoinjectors.
Indication: Hypercholesterolemia & mixed dyslipidemia
Due date: July 24, 2015

Recommendation for Approvability: The drug substance part of BLA 125559 is recommended for approval from a microbial control and microbiology product quality perspective

Review Summary
Sanofi has submitted BLA 125559 to license alirocumab drug substance and drug product and their manufacturing processes.

BLA 125559 was submitted in eCTD on November 24, 2014. This review contains the assessment of the manufacturing process of alirocumab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Colleen Thomas.

Amendments Reviewed for Drug Substance Quality

<table>
<thead>
<tr>
<th>Information Request date</th>
<th>Question numbers</th>
<th>Amendment sequence</th>
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<tbody>
<tr>
<td>January 16, 2015</td>
<td>1 to 8</td>
<td>February 13, 2015</td>
<td>0008</td>
</tr>
<tr>
<td>April 7, 2015</td>
<td>1, 2, 9</td>
<td>April 17, 2015</td>
<td>0033</td>
</tr>
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</table>
Review Narrative
S
S.1 DRUG SUBSTANCE
General Information
Alirocumab is a recombinant human IgG1 isotype monoclonal antibody with a molecular weight of 145,983 Da based on the . Alirocumab specifically binds to the proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. Alirocumab antagonizes PCSK9-mediated effects on LDL uptake by blocking the interaction of PCSK9 with the LDL receptor and lowers LDL cholesterol in vivo in a dose dependent manner.

Satisfactory

S.2 Manufacture
S.2.1 Manufacturer(s)
The following facilities are used for the manufacture, release testing, and stability testing of alirocumab drug substance:

Reviewer comments:
Refer to the cGMP status section of this review for the compliance status of .

S.2.2 Description of the Manufacturing Process and Process Controls
S.2.2.1 Batches and Scale Definition

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