CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s000

CHEMISTRY REVIEW(S)

First Approval for Indication
Expedited or Breakthrough Review

Recommendation: Approval

BLA 761055
Review Date: March 8, 2017

Drug Name/Dosage Form	**Dupilumab / injection**
Strength/Potency	**150 mg/mL**
Route of Administration	**Subcutaneous**
Rx/OTC Dispensed	**RX**
Indication	**Atopic Dermatitis (AD)**
Applicant/Sponsor	**Regeneron Pharmaceuticals Inc.**

Product Overview

Dupilumab is a human monoclonal immunoglobulin G 4κ antibody (IgG4κ), anti-interleukin-4 receptor alpha (IL-4Rα), produced in Chinese hamster ovary cells (CHO). It binds to the IL-4Rα subunit which is shared by IL-4 and IL-13 receptor complexes and inhibits of both the IL-4 and the IL-13 signaling cascades.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (DS)	Gunther Boekhoudt	DBRR IV/OBP
Drug Product (DP)	Xuhong Li	DBRR IV/OBP
Facilities	Wayne Seifert/ Peter Qiu	DIA/OPF
Microbiology DS	Maria Jose Lopez Barragan/ Reyes Candau Chacon	DMA/OPF
Microbiology DP	Lakshmi Narasimhan/ Patricia Hughes	DMA/OPF
Labeling	Jibril Abdus-Samad	OBP
Immunogenicity	Cristina Ausin-Moreno	DBRR IV/OBP
Business Regulatory Process Manager	Melinda Bauerlien	OPRO
Application Technical Lead	Cristina Ausin-Moreno	DBRR IV/OBP

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Matthew White	DDDP
Cross-disciplinary Team Lead	Snezana Trajkovic	DDDP
Medical Officer	Brenda Carr	DDDP
Pharm/Tox	Renqin Duan	DDDP
Clinical Pharmacology	Jack Wang/Dhananjay Marathe	OCP
Statistics	Carin Kim	DB III

a. Names
   i. Proprietary Name: dupixent
   ii. Trade Name: dupixent
   iii. Non-Proprietary/USAN: dupilumab
   iv. CAS number: 1190264-60-8
   v. INN Name: dupilumab
   vi. Common name: REGN668/SAR231893
   vii. OBP systematic name: MAB HUMAN (IGG4) ANTI P24394 (IL4RA_HUMAN) [REGN668]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody (IgG4); anti-human interleukin 4 receptor (IL-4rα); Immunomodulator interleukin inhibitor

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 761055/0003	6/29/2016
STN 761055/0004 (final rolling submission)	7/29/2016
STN 761055/0007 (response to IR #1)	8/12/2016
STN 761055/0009 (response to IR #2)	9/19/2016
STN 761055/0010 (DS manufacturing schedule)	9/23/2016
STN 761055/0011 (response to IR #3)	9/30/2016
STN 761055/0013 (response to IR #4)	10/24/2016
STN 761055/0016 (response to IR #5)	11/4/2016
STN 761055/0019 (plan for (b) (4) submission)	11/14/2016
STN 761055/0021 ((b) (4) submission and response to IR #6)	11/23/2016
STN 761055/0022 (immunogenicity IR)	11/28/2016
STN 761055/0023 (response to IR#7)	11/30/2016
STN 761055/0024 (follow up to response to IR#7)	12/2/2016
STN 761055/0025 (response to IR#9)	12/5/2016
STN 761055/0026 (response to IR#10)	12/6/2016
STN 761055/0027 (response to IR#11)	12/12/2016
STN 761055/0029 (response to IR#12)	12/30/2016
STN 761055/0030 (response to IR#14)	1/4/2017
STN 761055/0031 (withdrawal of (b) (4)	1/6/2017
STN 761055/0034 (withdrawal of (b) (4) – additional updates)	1/11/2017
STN 761055/0037 (response to IR#15)	1/25/2017
STN 761055/0038 (response to IR#16)	2/8/2017

Quality review Team – Signature Page

DISCIPLINE	REVIEWER	BRANCH/DIVISION	Signature
Drug Substance (DS)	Gunther Boekhoudt	Division of Biotechnology Review and Research IV	
Drug Product (DP)	Xuhong Li	DBRR IV	
Microbiology DS	Maria Jose Lopez Barragan	Division of Microbiology Assessment	
Microbiology DP	Lakshmi Narasimhan	DMA	
Facilities	Wayne Seifert	Division of Inspectional Assessment	
Immunogenicity	Cristina Ausin-Moreno	DBRR IV	
Microbiology Team Lead	Reyes Candau Chacon	DMA	
Microbiology Team Lead	Patricia Hughes	DMA	
Facilities Team Lead	Peter Qiu	DIA	
Application Technical Lead and DS and DP Team Lead	Cristina Ausin-Moreno	DMA	
Tertiary Reviewer	Michele Dougherty	DBRR IV (through 1/8/2017) OND/TBBS (effective 1/9/2017)	

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 II		(b) (4)	3	N/A (Not reviewed because sufficient information was included in the submission)	N/A	None
	Type III				Adequate	N/A	None
	Type V			2	Adequate	N/A	None
	Type V			2	Adequate	N/A	None
	Type III			3	N/A	N/A	None

[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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761055 for DUPIXENT manufactured by Regeneron Pharmaceuticals. The data submitted in this application are adequate to support the conclusion that the manufacture of DUPIXENT 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.

b. Draft action letter language

- Manufacturing location:
  - Drug substance – Regeneron Pharmaceuticals, Inc., 81 Columbia Turnpike, Rensselaer, NY (b) (4)
  - Drug product - Sanofi Winthrop Le Trait, 1051 Boulevard Industriel 76508 Le Trait, France
- Fill size and dosage form –
  - PFS: 300 mg/ 2 mL in prefilled syringe
  - PFS-S: 300 mg/ 2 mL in prefilled syringe assembled with a safety system
- Dating period:
  - Drug product – 24 months; 2-8ºC
  - (b) (4)
  - Drug substance – (b) (4) months; (b) (4) ºC

    Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
  - For stability protocols:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes; Rationale for exemption – specified product (exempted according to 601.2a)

c. Benefit/Risk Considerations

Dupilumab is a human IgG4 monoclonal antibody that binds to the IL-4 receptor alpha and inhibits IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). The proposed indication is for the treatment of adult patients with moderate-to-severe

atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

AD is a chronic and relapsing inflammatory skin disease characterized by intense pruritus and scaly and dry eczematous lesions. AD affects up to 25% of children and 2 to 3% of adults and is associated with up-regulations of IL-4 and IL-13.

Dupilumab was granted breakthrough designation on the basis of its apparent improved safety compared to available therapy.

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure process consistency and drug substance and drug product with appropriate quality attributes and free of adventitious agents.

The assays to detect anti-dupilumab antibodies are suitable for use in clinical studies. Overall, the data from the pivotal trials show that development of anti-drug antibodies (ADA) does not raise safety concerns. The presence of high ADA titers and neutralizing activity is associated with reduced dupilumab serum concentrations.

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. Revise the ≤ (b) (4) CFU(b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches has been analyzed.

2. Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL dupilumab drug product. Provide the data 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 (Type)	Risk	Origin	Control Strategy	Other
Cell based bioassay (potency)	Directly linked to efficacy	Intrinsic to molecule	(b) (4)	
Aggregates – High Molecular Weight Impurities (product related impurities)	Efficacy and safety	Introduced during manufacturing process and storage		
Low Molecular Weight Impurities (b) (4) (product related impurities)	Efficacy and safety	Introduced during manufacturing process and storage		
Charge variants (product related impurities)	Efficacy and safety	Introduced during manufacturing process and storage		
Higher Order Structure (potency)	Directly linked to efficacy and MOA	Intrinsic to molecule		

Glycosylation (potency and product related impurities)	Directly linked to efficacy and safety	Introduced during manufacturing process	(b) (4)	

B. Drug Substance: asfotase alfa Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes. For additional information see Appendix A for the Drug Substance and Drug Product Quality Review: OBP Assessment and Appendix B Microbiology Review: Division of Microbiology Assessment.

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	(b) (4)	
Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		
Host Cell Proteins (Process related impurity)	Safety and immunogenicity	Process; (b) (4)		
(b) (4) (Process related impurity)	Safety and immunogenicity	Process; (b) (4)		

Host cell DNA (Process related impurity)	Safety	Process; (b) (4)	(b) (4)	
(b) (4) (Process related impurity)	Safety	(b) (4)		
(b) (4) (Process related impurity)	Safety	(b) (4)		
(b) (4) (Process related impurity)	Safety	(b) (4)		
(b) (4) (Process related impurity)	Safety	(b) (4)		

(b) (4) (Process related impurity)	Safety	(b) (4)	(b) (4)	
(b) (4) (Process related impurity)	Safety			
(b) (4) (Process related impurity)	Safety	(b) (4)		
Viruses (Process related impurity)	Safety	Contamination during manufacture		
Leachables and extractables (Process related impurity)	Safety	Entire process		

a. Description
Dupilumab is human IgG4 κ antibody. The heavy chains contain 452 amino acids each, the light chains contain 219 amino acids and the hinge region has a serine to proline mutation at amino acid 233 to stabilize the interaction between heavy chains. The average molecular mass is 147 kDa. Each heavy chain contains a single N-linked glycosylation site at asparagine 302.

Molecular weight analysis confirmed identity and demonstrated lack of significant levels of post-translational modifications other than glycosylation. For additional information see Appendix A.

b. Mechanism of action
Atopic dermatitis is associated with type 2 immune responses. IL-4 and IL-13 are key cytokines required for the initiation and maintenance of the type 2 immune response. Dupilumab binds specifically to the human IL-4/IL-13 receptor (hIL-4Rα) and inhibits both IL-4 and IL-13 signal transduction.
For additional information see Appendix A.

c. Potency Assay
The biological function of dupilumab was characterized for its ability to bind to IL-4Rα by surface plasmon resonance-based Biacore and by in vitro cell based bioassays. These bioassays show that dupilumab is able to inhibit IL-4-mediated CD23 up-regulation in primary human B lymphocytes and in human Ramos Burkitt lymphoma cell line and also to inhibit IL-4-induced up-regulation of thymus and activation regulated chemokine in human embryonic kidney (HEK293) cell line. The function of the Fc domain was analyzed for its ability to promote complement-dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). Fc function is not detected.
Dupilumab binds to soluble IL-4rα with high affinity (K_D between 44.2 and 60.8 pM).
The potency release and stability assay uses the HEK293 cell line endogenously expressing IL-4Rα and engineered to express luciferase when stimulated with IL-4. Varying doses of dupilumab and a constant dose of hIL-4 are added to plates containing the HEK293 cells and incubated at 37°C to allow for binding prior to addition of luciferase. Dupilumab competes with hIL-4 inhibiting the bioluminescence reaction in a dose-dependent manner.
Dupilumab does not induce Fc mediated cytotoxicity (ADCC or CDC).
For additional information see Appendix A.

d. Reference material(s)
(b) (4)
Qualification and stability protocols were reviewed and found to be acceptable. For additional information see Appendix A.

e. Critical starting materials or intermediates

Cell bank system: (b) (4)

(b) (4)

(b) (4)

.

For additional information see Appendix A.

f. Manufacturing process summary

The manufacture of dupilumab drug substance (b) (4)

(b) (4)

(b) (4)

For additional information see Appendix A and Appendix B.

g. Container closure

(b) (4)

. For additional information see Appendix A and Appendix B.

h. Dating period and storage conditions
Drug Substance: (b) (4) months at (b) (4) °C

(b) (4)

C. Drug Product: Dupilumab 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 see Appendix A Drug Substance and Drug Product Technical Report: OBP Assessment and Appendix B Microbiology Review: Division of Microbiology Assessment.

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)	
Endotoxins (Contaminant)	Safety, purity and potential immunogenic reactions	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.		
Container Closure Integrity	Failure in closure integrity may lead to contamination (loss of	Might be impacted by storage		

(sterility assurance)	sterility) of DP or evaporation/leakage (impacting concentration or content)	conditions.	(b) (4)	
Protein concentration (general)	Variable protein concentration causes variable dosage of the drug and may affect efficacy	(b) (4)		
Clarity and color (general)	Safety and efficacy	Clarity may be impacted by the number of particles in solution; differences in color are indicative of contamination or degradation		
Particulate matter (Sub-visible particles (SVP)) (product or process related impurities)	Immunogenicity, patient safety	Container closure system (CCS) and process		
Foreign matter (visible particles) (product and process related impurities)	Immunogenicity, patient safety	Manufacturing material and CCS		
Leachables/	Safety	Manufacturing		

extractables (Process related impurities)		equipment and CCS	(b) (4)	
pH (general)	Safety and efficacy	Formulation		
Osmolality (general)	Safety	Formulation		
Extractable volume (general)	Essential for dosing	Manufacturing Process		
Identity (general)	Safety and efficacy	Intrinsic to molecule		

a. Potency and Strength
Dupilumab is supplied as a 300 mg/2 mL solution in a single-dose pre-filled syringe (PFS) with or without a safety system.
b. Summary of Product Design: Dupilumab is a sterile, preservative free, clear to slightly opalescent, colorless to pale yellow solution. Dupilumab is supplied in two presentations: a single-use prefilled syringe assembled with a safety system (PFS-S) and a single-use prefilled syringe without the safety system. Both syringes contain 2 mL of 150 mg/mL dupilumab.
c. List of Excipients: L-arginine hydrochloride (25 mM), L-histidine (20 mM), polysorbate 80 (0.2% (w/v)), sodium acetate (12.5 mM), sucrose (5% (w/v))
d. Reference material(s): the same reference material is used for drug substance and drug product
e. Manufacturing Process
The manufacturing process of drug product consists of (b) (4)
The control strategy is appropriate to ensure aseptic processing, consistently accurate fill and adequate critical quality attributes.
For additional information see Appendix A and Appendix B.
f. Container Closure
Dupilumab is supplied in two presentations. The bulk PFS is stored in a 2.25 mL clear glass syringe barrel with a 27 gauge (b) (4) needle, protected by a rigid needle shield and an (b) (4) plunger stopper (b) (4)
In the PFS presentation the bulk PFS is assembled with a plunger rod and a finger flange. In the PFS-S presentation the bulk PFS is assembled with a plunger rod and inserted in a safety system preassembled with a finger flange.
Appropriate compatibility studies were performed for the container closure system. For additional information see Appendix A and Appendix B.
g. Expiration Date & Storage Conditions: 24 months at 2-8°C
The data included in the BLA support storage for up to 14 days at 25°C once removed from refrigerator, as described in the labeling.
h. List of co-packaged components, if applicable: None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

Store at 2-8°C. Protect from light. Do not freeze or shake. Once removed from refrigeration it should be used within 14 days.

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
DS (b) (4) Manufacture In-process, release and stability testing	Regeneron Pharmaceuticals Inc.; Rensselaer, NY	945589711/ 1000514603		NAI	Approve
(b) (4)			Approve based on profile		Approve
			Approve based on profile		Approve
			Approve based on profile		Approve
DS (b) (4) in-process, and release testing		(b) (4)	Approve based on profile		Approve
DS release and stability testing			Approve based on profile		Approve

DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**		**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Manufacture of bulk PFS, PFS, and PFS-S **Packaging and labeling** **Release and stability testing**	**Sanofi Winthrop Industrie; Le Trait, France**	**297730488/ 3003259844**		**VAI** (b) (4)	**Approve**
DP secondary packaging and labeling	**Sanofi-Aventis US. LLC; Saint Louis, MO**	**011330557 /1000117606**			**No evaluation required**
DP release and stability testing	**Regeneron Pharmaceuticals Inc; Rensselaer, NY**	**945589711/ 1000514603**		**NAI**	**Approve**
DP release testing	(b) (4)		**Approve based on profile**		**Approve**
			Approve based on profile		**Approve**

	(b) (4)				
	Sanofi-Aventis Deutschland GmbH; Frankfurt am Main, Germany	**313218430/ 3003195501**	**Approve based on profile**		**Approve**

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G. Facilities

The inspection of the drug product manufacturing and testing facility, Sanofi Winthrop Industrie was conducted February 6-14, 2017 by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the drug substance manufacture and testing facility, Regeneron Pharmaceuticals Inc. was conducted October 31- November 4, 2017 by CDER/OPQ and was classified NAI.

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

H. Lifecycle Knowledge Management

a. **Drug Substance**

i. Protocols approved

- (b) (4) validation to be reported in AR
- Annual stability protocol for DS (b) (4)

b. **Drug Product**

i. Protocols approved

- Annual stability protocol
- Stability protocol for the extension of shelf-life to up to 36 months

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_____			X
	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		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		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
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 _____				X

Appendices

BLA STN 761055

Product USAN name
Dupilumab

Manufacturer
Regeneron Pharmaceuticals, Inc.

Reviewer: Gunther Boekhoudt
Reviewer: Xuhong Li (Drug Product)
Cristina Ausin (Immunogenicity)
TL: Cristina Ausin
RC: Michele Dougherty
Office of Biotechnology Products
Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. **BLA#: STN 761055**

2. **REVIEW DATE:**

3. **PRIMARY REVIEW TEAM:**

Clinical TL:	**Snezana Trajkovic**
Clinical Reviewer:	**Brenda Carr**
Clinical Pharmacology TL:	**Yow-Ming Wang**
Clinical Pharmacology:	**Jie Wang**
Clinical Pharmacometrics:	**Renqin Duan**
Product Quality TL:	**Cristina Ausin**
Product Quality Reviewer:	**Gunther Boekhoudt**
Product Quality Reviewer (Drug Product):	**Xuhong Li**
Product Quality Reviewer (Immunogenicity):	**Cristina Ausin**
Product Quality Labeling Reviewer:	**Jibril Abdus-Samad**
Micro TL:	**Patricia Hughes**
Micro Reviewer:	**Lakshmi Rani Narasimhan**
Non Clinical:	**Renqin Duan**
Non Clinical TL:	**Barbara Hill**
Facilities Reviewer:	**Zhihao Peter Qiu**
Statistics:	**Carin Kim**
Statistics TL:	**Mohamed Alosh**
Compliance Officer:	**Wayne Seifert**
Center for Devices and Radiological Health:	**Sapana Patel**
Center for Devices and Radiological Health TL:	**Alan Stevens**
Drug Use Analyst:	**Marlene Schultz-Depalo**
RBPM:	**Matthew White**

4. **MAJOR GRMP DEADLINES**

Received:	**June 29, 2016**
Filing Meeting:	**September 2, 2016**
Mid-Cycle Meeting:	**October 28, 2016**
Primary Review Due:	**December 9, 2016**
Secondary Review Due:	**January 9, 2017**
Wrap-Up Meeting:	**February 2, 2017**
CDTL Memo Due:	**February 12, 2017**
PDUFA Action Date:	**March 29, 2017**

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

Communication/Document	Date
Pre-BLA Meeting	12/16/2015 (cancelled; preliminary comments sent on 12/07/2016)
CMC Pre-BLA Meeting	2/24/2016

Information Request #3 (immunogenicity and DS manufacturing schedule)	9/20/2016
Midcycle Meeting	10/28/2016
Information Request #5 (OBP DS)	11/1/2016
Midcycle Communication with Sponsor	11/9/2016
Information Request #6 (Stability update and DMA DP)	11/16/2016
Information Request #7 (OBP DS and DP)	11/22/2016
Information Request #11 (OBP DS and DP)	12/6/2016

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

Submission	Date Received	Review Completed (Yes/No)
STN 761055/0004	7/29/2016	Yes
STN 761055/0010 (response to IR3)	9/23/2016	Yes
STN 761055/0016 (response to IR5)	11/4/2016	Yes
STN 761055/0021 (response to IR6)	11/23/2016	Yes
STN 761055/0023 (response to IR7)	11/30/2016	Yes
STN 761055/0024 (response to IR7)	12/2/2016	Yes
STN 761055/0027 (response to IR11)	12/12/2016	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Dupixent
   b. Trade Name: Dupixent
   c. Non-Proprietary/USAN: Dupilumab
   d. CAS name: 1190264-60-8
   e. Common name: REGN668, SAR231593
   f. INN Name: Dupilumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMAN (IGG4) ANTI P24394 (IL4RA_HUMAN) [REGN668]
   i. Other Names: Anti-human interleukin-4 receptor subunit alpha

8. **PHARMACOLOGICAL CATEGORY:** Monoclonal antibody
9. **DOSAGE FORM:** Injection
10. **STRENGTH/POTENCY:** 150 mg/mL (2.25 mL PFS)
11. **ROUTE OF ADMINISTRATION:** Subcutaneous (SC)
12. **REFERENCED MASTER FILES:** None for drug substance
13. **INSPECTIONAL ACTIVITIES:**
Drug substance site inspection (Rensselaer, NY) initiated October 31, 2016 and completed November 5, 2016. No 483 items provided.
14. **CONSULTS REQUESTED BY OBP:** None
15. **QUALITY BY DESIGN ELEMENTS:** None

16. PRECEDENTS: None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Michele Dougherty, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV (through 1/7/2017) Science Policy Analyst OND/TBBS (effective 1/8/2017)	
Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV	
Gunther Boekhoudt, Ph.D., Primary Reviewer (Drug Substance) Division of Biotechnology Review and Research IV	

B. CC Block

Recipient	Date
Matthew White	January 3, 2017
Division of Biotechnology Review and Research IV File/BLA STN 761055	January 3, 2017

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

From the Chemistry, Manufacturing Controls perspective, BLA 761055 is recommended for approval.

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

Environmental Assessment or Claim Of Categorical Exclusion (BLA section 1.12.14)
The Sponsor claims a categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(c). Thus, no environmental assessment needs to be performed.
The Sponsor's claim for Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review

Draft package labeling review provided by Jibril Abdus-Samad. See attached.

VI. Review Of Common Technical Document-Quality Module 3.2

Review of CTD Module 3 provided. See below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Review of immunogenicity assays provided by Cristina Ausin. See attached.

VIII. EDR Location:

STN 761055

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

Dupilumab is a human monoclonal immunoglobulin G 4κ antibody (IgG4κ), anti-Interleukin-4 receptor α chain (IL-4Rα), produced in Chinese hamster ovary cells (CHO). It binds to the common IL-4Rα chain of both the IL-4 and IL-13 signaling cascade and therefore is an inhibitor of both IL-4 and IL-13 signaling. The molecule consists of a 452 amino acids heavy chain (HC) and a 219 amino acids light chain (LC) with an average molecular mass of 147 kDa. The hinge sequence of the IgG4 molecule has a serine-to-proline mutation at amino acid 233 to stabilize the interaction between the heavy chains. The HC constant region 2 (CH2) domain of the crystallisable fragment (Fc) of the HC contains a single N-linked glycosylation site at asparagine 302. The amino acid sequence and graphic representation of dupilumab are shown below in Figure S.1.2-1 and Figure S.1.2-2, respectively.

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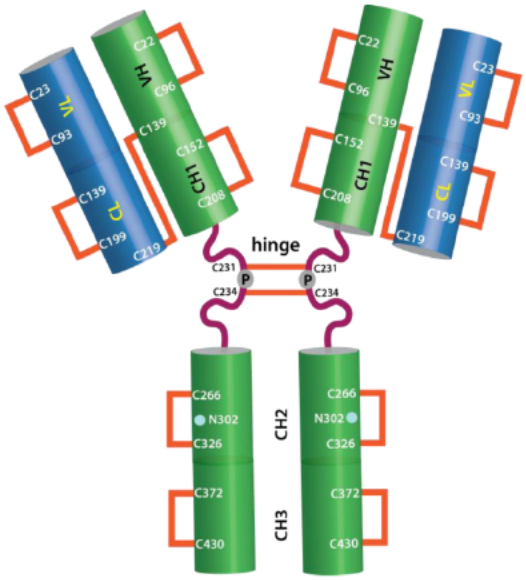
Figure S.1.2-1 Dupilumab Amino Acid Sequence

Sequence of dupilumab heavy chain and light chain with the CDRs highlighted in blue. The cysteine residues (red) that have been confirmed to form predicted disulfide bonds are connected by solid orange lines. The Fc N-linked glycosylation site at Asn^{302} is in green. The heavy chain C-terminal Lys^{452} (pink) is predominantly removed during protein expression. Within the heavy chain hinge region, Ser^{233} (WT IgG4) has been mutated to Pro^{233} (cyan) to promote stabilization of the dupilumab IgG4 molecule. This mutation stabilizes the inter-chain disulfide bonds between two heavy chains, and minimizes the potential for generating half-antibody, product-related forms.

Figure S.1.2-2 Dupilumab Amino Acid Sequence



Representation of the structure of dupilumab, 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). The hinge region mutation (Ser^{233} to Pro^{233}) is located between the two hinge region disulfide bonds and is shown as a "P".
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

3.2.S.1.3 General Properties

Dupilumab functions by binding to the IL4Rα and blocking the downstream signaling of both the IL-4 and IL-13 pathway. Detailed physicochemical and biochemical are discussed above and throughout this review.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Manufacturing and testing laboratories of dupilumab are listed below in Table S.2.1-1.

Reviewer Comment: *Manufacturers and their responsibility were provided and the information is sufficient.*

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BLA 761055

Dupixent (Dupilumab)

Manufacturer:

Regeneron Pharmaceuticals, Inc

81 Columbian Turnpike

Rensselaer, NY 12144

Xuhong Li, Ph.D., Quality Reviewer (DP)
Cris Ausin, Ph.D., Team Lead

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

OBP CMC Review Data Sheet

1. **BLA#:** STN 761055

2. **REVIEW DATE:**

3. **PRIMARY REVIEW TEAM:**

Clinical TL:	**Snezana Trajkovic**
Clinical Reviewer:	**Brenda Carr**
Clinical Pharmacology TL:	**Yow-Ming Wang**
Clinical Pharmacology:	**Jie Wang**
Clinical Pharmacometrics:	**Renqin Duan**
Product Quality TL:	**Cristina Ausin**
Product Quality Reviewer (Drug Substance):	**Gunther Boekhoudt**
Product Quality Reviewer (Drug Product):	**Xuhong Li**
Product Quality Reviewer (Immunogenicity):	**Cristina Ausin**
Product Quality Labeling Reviewer:	**Jibril Abdus-Samad**
Micro TL:	**Patricia Hughes**
Micro Reviewer (Drug Substance):	**Maria Jose Lopez Barragan**
Micro Reviewer (Drug Product):	**Lakshmi Rani Narasimhan**
Facilities Reviewer:	**Zhihao Peter Qiu**
Compliance Officer:	**Wayne Seifert**
Drug Use Analyst:	**Marlene Schultz-Depalo**
RBPM:	**Matthew White**

4. **MAJOR GRMP DEADLINES**

Received:	**June 29, 2016**
Filing Meeting:	**September 2, 2016**
Mid-Cycle Meeting:	**October 28, 2016**
Primary Review Due:	**December 9, 2016**
Wrap-Up Meeting:	**February 21, 2017**
PDUFA Action Date:	**March 29, 2017**

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

Communication/Document	Date
Pre-BLA Meeting	12/16/2015 (cancelled; preliminary comments sent on 12/07/2016)
CMC Pre-BLA Meeting	2/24/2016
Information Request #3 (immunogenicity and DS manufacturing schedule)	9/20/2016
Midcycle Meeting	10/28/2016
Information Request #5 (OBP DS)	11/1/2016

Midcycle Communication with Sponsor	11/9/2016
Information Request #6 (Stability update and DMA DP)	11/16/2016
Information Request #7 (OBP DS and DP)	11/22/2016
Information Request #11 (OBP DS and DP)	12/6/2016

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

Submission	Date Received	Review Completed (Yes/No)
STN 761055/0004	7/29/2016	Yes
STN 761055/0010 (response to IR3)	9/23/2016	Yes
STN 761055/0016 (response to IR5)	11/4/2016	Yes
STN 761055/0021 (response to IR6)	11/23/2016	Yes
STN 761055/0023 (response to IR7)	11/30/2016	Yes
STN 761055/0024 (response to IR7)	12/2/2016	Yes
STN 761055/0027 (response to IR11)	12/12/2016	Yes

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

a. Proprietary Name: Dupixent
b. Trade Name: Dupixent
c. Non-Proprietary/USAN: Dupilumab
d. CAS name: 1190264-60-8
e. Common name: REGN668, SAR231593
f. INN Name: Dupilumab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMAN (IGG4) ANTI P24394 (IL4RA_HUMAN) [REGN668]
i. Other Names: Anti-human interleukin-4 receptor subunit alpha

8. **PHARMACOLOGICAL CATEGORY:** Monoclonal antibody
9. **DOSAGE FORM:** Injection
10. **STRENGTH/POTENCY:** 150 mg/mL (2.25 mL PFS)
11. **ROUTE OF ADMINISTRATION:** Subcutaneous (SC)
12. **REFERENCED MASTER FILES:** None for drug substance
13. **INSPECTIONAL ACTIVITIES:**

Drug product site inspection (Le Trait, France) scheduled for February 6-13, 2017.

14. CONSULTS REQUESTED BY OBP: None
15. QUALITY BY DESIGN ELEMENTS: None
16. PRECEDENTS: None
17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date

Michele Dougherty, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV	
Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV	
Xuhong Li, Ph.D.., Primary Reviewer (Drug Product) Division of Biotechnology Review and Research IV	

B. CC Block

Recipient	Date
Matthew White	
Division of Biotechnology Review and Research IV File/BLA STN 761055	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

From the Chemistry, Manufacturing Controls perspective, BLA 761055 is recommended for approval.

Note: The applicant submitted a major amendment on 11/23/2016 to include the (b) (4) (b) (4) as an (b) (4). The information was withdrawn on 01/06/2017 to restore the original PDUFA date for the submission. Since the drug product quality review has already completed for the (b) (4) (b) (4) the evaluation for the (b) (4) (b) (4) is kept in the drug product review as a reference.

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

Environmental Assessment or Claim Of Categorical Exclusion (BLA section 1.12.14)
The Sponsor claims a categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(c). Thus, no environmental assessment needs to be performed.
The Sponsor's claim for Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review

Draft package labeling review provided by Jibril Abdus-Samad.

VI. Review Of Common Technical Document-Quality Module 3.2

Review of CTD Module 3 provided. See below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Review of immunogenicity assays provided by Cristina Ausin.

VIII. EDR Location:

STN 761055

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P DRUG PRODUCT

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

Dupilumab drug product is supplied as a single-use prefilled syringe (PFS) or a single-use prefilled syringe assembled with a safety system (PFS-S). Each prefilled syringe contains 2 mL of 150 mg/mL dupilumab solution, a clear to slightly opalescent, colorless to pale yellow, (b) (4), sterile solution, pH 5.9, for subcutaneous (SC) administration. The entire contents in the syringe are intended to be injected, providing a 300 mg dose of dupilumab. The nominal composition of the dupilumab solution for injection is as follows:

Table 1 Composition of Dupilumab Solution for Injection

Component	Function	Reference to Quality Standard	Drug Product Nominal Composition	Nominal Amount per Prefilled Syringe (mg)[a]
Dupilumab	Active pharmaceutical ingredient	Custom specification	150 mg/mL	300
L-Histidine (b) (4)	(b) (4)	USP, Ph. Eur., JP	20 mM	6.2[b]
		Ph. Eur., JP		
L-Arginine (b) (4) ydrochloride		USP, Ph. Eur., JP	25 mM	(b) (4)
Sodium Acetate (b) (4)		USP, Ph. Eur., JP	12.5 mM	
(b) (4)		USP, Ph. Eur., JP		
Sucrose		NF, Ph. Eur., JP	5% (w/v)	100
Polysorbate 80		NF, Ph. Eur., JP	0.2% (w/v)	4
Water for Injection		USP, Ph. Eur.	(b) (4)	

[a] Based on a 2.0 mL injection volume

[b] Reported as milligrams histidine base (MW = 155.16 g/mol), calculated assuming a molar concentration of 20 mM histidine

(b) (4)

USP, United States Pharmacopeia; NF, National Formulary; Ph. Eur., European Pharmacopeia; JP, Japanese Pharmacopeia

The primary container closure system is a siliconized, 2.25 mL, clear Type 1 glass syringe barrel, equipped with a staked, stainless steel, 27 G, 1/2" 3B, thin-walled needle, with a grey (b) (4) plunger stopper, and a grey (b) (4) needle shield, designated "soft needle shield (SNS), form the complete (b) (4) PFS primary container closure system. The (b) (4) needle shield may be supplied with or without a transparent rigid (b) (4) cap, designated "rigid needle shield (RNS)". The drug product in the primary container is named "bulk PFS'.

Each PFS or PFS-S presentation is comprised of a bulk PFS, a (b) (4) plunger rod (transparent for PFS and white for PFS-S) to allow delivery of the syringe contents, and a white (b) (4) finger flange to facilitate handling. The PFS-S presentation also has a safety system for sharps injury prevention. The safety system consists of a (b) (4) needle guard

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

Memorandum of Review:

STN:	BLA 761055
Subject:	Immunogenicity Review
Date:	July 28, 2016
Review/Revision Date:	December 6, 2016 / January 18, 2017
Primary Reviewer:	Cristina Ausin-Moreno, Ph.D.
Secondary Reviewer:	Michele Dougherty, Ph.D.
Applicant:	Regeneron
Product:	Dupilumab
Indication:	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Filing Action Date:	September 27, 2016
Action Due Date:	March 29, 2017

I. Executive Summary:

Binding antibodies are measured using an electrochemiluminescence (ECL) assay in a bridging format. The cut points are established according to current FDA guidance, the sensitivity is significantly higher than that recommended in the current guidance (9.9 vs.100 ng/mL), and the drug tolerance is above the expected dupilumab serum concentration of 74 µg/mL at concentrations of positive controls between 150 and 500 ng/mL.

Neutralizing antibodies (NAbs) are detected using a competitive ligand binding assay. The sensitivity is within the typical range for NAb assays; however, the validated drug tolerance is significantly lower than the expected dupilumab concentration in the samples. Because the NAb assay is able to detect NAbs even in the presence of high binding antibody titers and, according to the clinical pharmacology team, the PK assay is adequate to quantify differences in dupilumab concentration in serum that may be caused due to the presence of NAbs, the low drug tolerance of the NAb assay does not constitute a safety concern.

II. Review:

Introduction

Dupilumab (REGN668) is a human IgG4κ monoclonal antibody produced in CHO cells that binds specifically with high affinity to the IL-4 receptor alpha subunit, thus blocking IL-4 and IL-13 signaling. Under BLA 761055 (IND 107969), dupilumab is being developed for the treatment of atopic dermatitis (AD) by SC administration.

AD is a systemic inflammatory allergic disease of the skin characterized by intense pruritus and scaly, dry eczematous lesions. AD is associated with a type 2 immune response that involves both the innate and the adaptive immune systems. Because activation of IL-4 and IL-13 signaling precedes the release of pro-inflammatory mediators, the sponsor developed dupilumab as an antagonist of these two cytokines to reduce the type 2 inflammatory responses characteristic of AD.

The sponsor provided reports corresponding to three phase 3 clinical studies. These include a randomized, double-blind, placebo-controlled study of 52-week concomitant treatment with topical corticosteroids (r668-ad-1224) and two replicate, randomized, double-blind, placebo-controlled, confirmatory, monotherapy, 16-week treatment studies (r668-ad-1334 and r668-ad-1416). All three studies assessed safety and efficacy in patients with moderate-to-severe AD whose disease was not adequately controlled with topical medication.

Total Antibodies Assay

The bioanalytical method uses an electrochemiluminescence (ECL) assay in a bridging format. The sponsor uses REGN1097 (mouse anti-REGN668) as a positive control and biotinylated REGN668 and ruthenium-labeled REGN668 as the bridge components. The plates are coated with streptavidin to capture the biotinylated REGN668. In presence of the positive control or ADA, a bridge is formed because the anti-REGN668 antibodies bind to both BioREGN668 and Ru-REGN668. The bound complexes are detected by an ECL signal generated by the Ru label. The measured ECL signal is proportional to the amount of ADA present in the sample.

The method is a non-quantitative, titer-based assay involving three tiers:

1. Initial screening assay to identify samples that are potentially positive for anti-drug antibodies (ADA).
2. Confirmation assay to determine if a positive response in the screening can be inhibited by the presence of excess unlabeled drug.
3. Titer assay to assess levels of ADA in samples positive in the confirmation assay.

The original assay (validation report regn668-av-09106-va-01v2, reviewed by Carla Lankford, reviews uploaded in DARRTS under IND 107969 [redacted] (b) (4)) had a drug tolerance limit

that was below the steady state trough drug concentration. The sponsor modified the assay to be able to detect ADA in the presence of the expected levels of dupilumab in AD patient sera. The modification consisted in the introduction of an acid treatment of serum samples prior to analysis, to dissociate antibody-drug complexes.

The revised assay was used in the phase 3 studies conducted to support licensure under the current BLA (r668-ad-1224, r668-ad-1334, and r668-ad-1416). The assay validation report (regn668-av-13089-va-01v1) was reviewed by Gunther Boekhoudt and the information was deemed acceptable to support the adequacy of the assay in terms of specificity, sensitivity, precision, linearity, analyte stability, robustness, and ruggedness (reviews uploaded in DARRTS on February 4, 2015 and October 29, 2015).

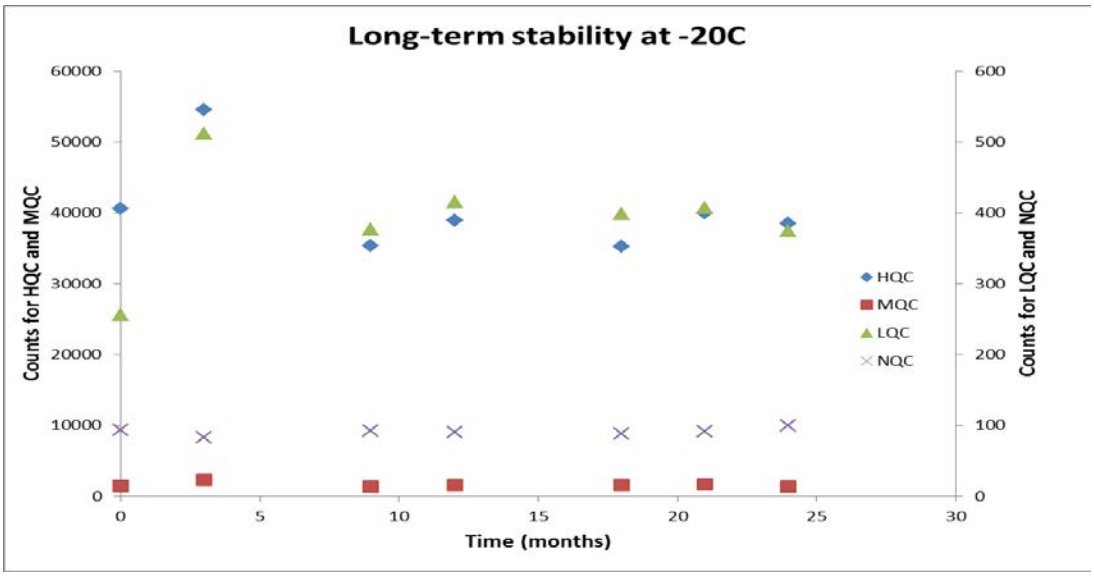
At the time of the BLA submission, the sponsor amended the validation report to include results from long term stability (LTS) testing, add population specific cut point factors (CF) for atopic dermatitis and asthma, and re-analyze the sensitivity and the drug tolerance levels (DTL) using the revised cut point factors determined using additional baseline serum samples from atopic dermatitis and asthma populations. The current review will evaluate only the new sections included in validation report regn668-av-13089-va-01v2.

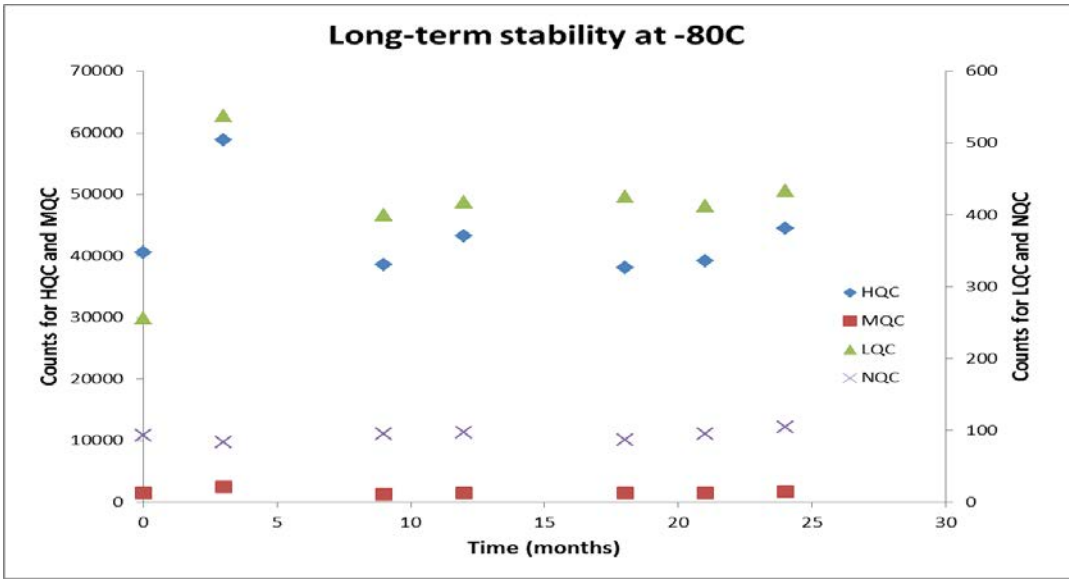
1. Long-term stability testing:

The sponsor stored quality controls (QCs) (high (HQC), medium (MQC), low (LQC), and negative (NQC)) at -20°C and -80°C, tested them after 3, 9, 12, 18, 21, and 24 months, and compared the results to those of freshly prepared samples. The mean count results were expressed as relative to the freshly prepared samples. The following table (excerpted from Validation Summary table in report regn668-av-13089-va-01v2) contains a summary of the stability results. Complete results are included in tables 24 and 25 of the report.

Assay/Validation Parameters	Result
Analyte Stability QCs %AR ≥ 75%, CV% Counts ≤ 20% (MQC titer of stability MQCs must fall within one dilution factor of the control MQC Titer)	
4°C Overnight	113-119%, 2-4% 99-106%, 2-6%
4 hours Room Temperature	79-112%, 0-5%
10X Freeze/Thaw Cycles	
Long-term storage in a -20°C freezer	125-186%, 0-15%- **24 months**
MQC Titer	960 - 1920 (within one dilution of control MQC)
Long-term storage in a -80°C freezer	123-207%, 0-10% - **24 months**
MQC Titer	960 - 3840 (within one dilution of control MQC)

Reviewer's comment: *The titers for the stability samples are in all cases higher than or the same as the titers for the control, this indicates that storage at -20°C and -80°C does not have a negative effect on the stability of the controls. There appear to be differences with time in the titers measured for the stability and control samples, which could indicate assay variability. However, a graphical analysis of the data indicates that the results for the 3 month time point are an outlier for both storage conditions, while all the other results are significantly more consistent. The counts for the negative control (not reproduced in this review) are low and consistent, which is indicative of good assay sensitivity. The sponsor provided sufficient information to support the stability of the QCs for 24 months at -20°C and -80°C.*





2. Cut points re-evaluation for AD and asthma patients

During the original validation, the sponsor used samples from 54 AD patients to determine the screening, confirmation, and titer cut point factors (CF). Gunther Boekhoudt concluded that all cut points had been established correctly, with the appropriate percentage of false positive cases. After the original assay validation was completed, the sponsor analyzed baseline samples from 571 AD patients and re-evaluated the CF values. The results are provided in report regn668-mx-15116-sr-01v1.

For the screening cut point, a statistical analysis was performed on the log-transformed S/N ratio of all 1142 values obtained for the samples of those 571 patients. This analysis justified the elimination of analytic (11) and biologic (59) statistic outliers. The sponsor determined a non-parametric floating screening CF of 1.44 based on an empirical 95th percentile for the log-transformed S/N ratio values, in agreement with the Agency's recommendation of a 5% false positive ratio.

To re-evaluate the confirmatory CF for the AD patients, the sponsor selected 80 of the new patient samples with the highest S/N ratios in the screening assay. The samples were analyzed in the presence and absence of 50 µg/mL dupilumab. Maintaining the same CF of 28% that was calculated during the original validation, after eliminating the outliers, one sample had a percent inhibition above the CF, in agreement with the Agency's suggested minimum of 1% false positive error rate.

The titer CF was calculated based on the 99.9th percentile of the S/N. The sponsor determined a parametric floating titer cut point factor of 1.64.

The following table contains a summary of the CF results:

	Original Validation	**Revised for AD patients**	**Revised for Asthma Patients***
Screening CF	1.28	1.44	(b) (4)
Confirmation CF	28%	28%	
Titer CF	1.47	1.64	

(b) (4)

Reviewer's comment: *Evaluation of all the reported results indicates that after eliminating the outliers, the rate of false positives for the screening assay is 4.9%, which is in agreement with*

FDA's recommendation of 5%. Including the outliers, the rate of false positives is 10%, which would correspond to an over conservative evaluation and supports the proposed screening CF.

The clin-pharm reviewers are concerned about the high percentage of patients with ADA incidences in the placebo treatment groups and high pre-existing ADA at baseline and they are wondering if it would be necessary to re-evaluate the cut point of the immunogenicity assay.

(b) (4) *This strategy may be an option for the AD patients as well.*

The sponsor was asked to provide a justification for the number of ADA positive samples at baseline and to consider evaluating if the positive samples at baseline are due to ADA that are not specific to dupilumab, (b) (4) *. In their response submitted on November 28, 2016 (Sequence number 0022), the sponsor claimed that the high number of biological outliers is the reason for the unusual results. Including the biological outliers the screening and the confirmatory assays' false positive rates are 10% and 3%, respectively, which is higher than the required 5% and 1%.). In addition, the sponsor explained that in the case of the AD patients the baseline titers are all low,* (b) (4) .

The information provided by the sponsor is adequate to support the proposed cut points.

3. Re-analysis of sensitivity and drug tolerance using the new CF values

The sponsor re-evaluated the sensitivity and the drug tolerance by re-analyzing the results obtained during the original validation using the updated CF values. The following table contains a summary of the revisions:

Patient Population	Control	Original Value	Re-evaluated Value
Sensitivity (in neat serum)			
Atopic Dermatitis	Positive Control	6.9 ng/mL	9.9 ng/mL
	Polyclonal Ab Control	1.0 ng/mL	1.6 ng/mL
Asthma	Positive Control	(b) (4)	
	Polyclonal Ab Control		
Drug Tolerance (in neat serum) at 500 ng/mL			
Atopic Dermatitis	Positive Control	316 µg/mL	251 µg/mL
	Polyclonal Ab Control	763 µg/mL	635 µg/mL

Asthma	Positive Control		(b) (4)
	Polyclonal Ab Control		

Reviewer's comment: *The revision of the cut point factors due to the inclusion of serum samples from more patients caused a slight decrease in both sensitivity and drug tolerance. The sensitivity is still well below the Agency's recommendation of 100 ng/mL and is therefore, acceptable.*
Regarding the drug tolerance results, during the November 4, 2015 meeting, the sponsor was advised to re-evaluate the drug tolerance at ADA levels in serum lower than 250 ng/mL as follows:

"You have assessed drug tolerance of ADA assay # 1 at 250 ng /ml and 500 ng/ ml control antibody. In order to understand the effect of on-board REGN2339 on low but detectable patient antibody levels, you should assess drug tolerance of ADA assays #1 and # 2 at control antibody concentrations lower than 250 ng/ ml."

Sponsor's response: "As requested, the Sponsor will assess the effect of on board drug (dupilumab) on detection of lower levels of anti-drug antibodies. Drug (dupilumab) tolerance will be assessed at concentrations lower than 250 ng/mL of positive control antibody (REGN1097) for both ADA assay #1 and #2. This information will be provided in the updated validation report for assay #1 at the time of the AD BLA filing."

I was not able to find this information in the revised validation report. The measured titers are mostly low or intermediate, so it is important to confirm that they are truly low and that the presence of on board drug is not causing artificially low results. According to the PK data from study r668-ad-1224, the steady state trough drug concentration for the biweekly treatment is 76.7 µg/mL. According to the draft labeling, (b) (4)

The following IR was sent to the sponsor on September 20, 2016:

> *In the reports for clinical studies r668-ad-1224, r668-ad-1334, and r668-ad-1416 you indicate that most of the ADA titers measured in patients are low or moderate. To demonstrate that the ADA assay is able to properly detect and quantify low antibody levels it is necessary to assess the drug tolerance of the assay at those low ADA levels. During the November 4, 2015 meeting you committed to assess on board drug (dupilumab) tolerance at positive control antibody concentrations lower than 250 ng/mL and to provide the information in the updated validation report at the time of the atopic dermatitis BLA filing. According to report regn668-av-13089-va-01v2, upon revision of the screening and titer cut points, you re-evaluated the assay's drug tolerance at a positive control antibody concentration of 500 ng/mL in serum. Clarify where drug*

tolerance data at positive control antibody concentrations lower than 250 ng/mL are included in the report or submit the information.

In BLA amendment 0011 submitted September 30, 2016, the sponsor provided the following DTL values for lower concentrations of the positive control antibodies:

Table 1: Drug Tolerance – REGN1097 and REGN2339 at 150 ng/mL and 200 ng/mL

	Monoclonal Antibody Positive Control (REGN1097)		Rabbit Polyclonal Anti-REGN668 Antibody (REGN2339)	
	150 ng/ml	200 ng/mL	150 ng/ml	200 ng/mL
DTL (µg/mL)	131.3	154.9	333.0	397.8

Reviewer's comment:
As requested, the sponsor evaluated the drug tolerance at lower levels of positive control antibodies. The incidence of ADA positive cases indicates that the assay is able to detect antibodies in the presence of drug concentrations measured in patients. In the case of the single patient with a high titer signal, the presence of ADA seems to cause a significant drop in the PK measurement. For all other patients, there seems to be a lower PK signal than for ADA negative patients, however, due to the variability of the results, the clin-pharm reviewers are not able to conclude if the difference is significant. The evaluation of the clinical effect of the presence of ADA is deferred to the clinical and clin pharm reviewers.

4. Automated execution of the assay

In BLA amendment 0004 submitted July 29, 2016, the sponsor provided a report to demonstrate the verification of the performance of the screening and confirmation assays using an automation system. The automation system controls the scheduling and pipetting software and all the integrated instruments.

The verification of the automation of the screening assay is provided in report aav-lor13577-pcl3400-r1. QCs and clinical samples were used in the cross-validation exercises. The sponsor first verified the suitability of the QC samples:

- LQC mean counts > plate cut point
- HQC mean counts > MQC Mean Counts > LQC Mean counts
- CV% counts for each PQC ≤ 20% (results between 1 and 6%)
- CV% of the mean counts for each PQC ≤ 20% (results between 3 and 6%)

During the cross validation, the sponsor evaluated the agreement in results by analyzing 50 antibody-positive and 10 antibody-negative samples and got the same results using the manual

and the automation system. In addition, acceptable precision was demonstrated with reproducible results obtained after analysis of multiple antibody-positive and antibody-negative clinical samples, over multiple plates, in two independent automation runs, over two days.

% Agreement (for all samples) = 100 x (Number of Matched Results/Total Results)

% Reproducibility = 100 x (Number of Samples with acceptable %Agreement/Total Number of Samples)

% agreement and % reproducibility were 100% in all cases. The CV% Counts were between 0 and 10%, which was in agreement with the acceptance criterion of ≤ 20% and with the inter-plate precision demonstrated during validation of the manual assay (10-11%).

The verification of the automation of the confirmation assay is provided in report avv-lor13577-pcl3400-r2. QCs and clinical samples were used in the cross-validation exercises. The sponsor first verified the suitability of the QC samples:

- LQC mean counts > plate cut point
- HQC mean counts > MQC Mean Counts > LQC Mean counts
- CV% counts for each PQC ≤ 20% (results between 1 and 7%)
- CV% of the NQC ≤ 25%
- CV% of the mean counts for each PQC ≤ 20% (results between 6 and 13%)

40 ADA positive clinical samples were reanalyzed manually and all 40 were confirmed positive. The same samples were tested using the automation system and 37 were confirmed positive, which constitutes a 93% agreement. The CV% counts ranged from 0 to 17% for the automated analysis and between 0 and 18% for the manual analysis.

Precision was confirmed analyzing the results from 15 confirmed ADA positive samples in four sets, run in 4 plates (two plates per run, over two different days). 14 out of 15 samples were confirmed positive in all 4 plates and the remaining sample was confirmed positive in one of the four plates. The CV% Counts for all samples ranged between 0 and 16%, which is in agreement with the variability seen in the manual analysis.

Reviewer's comment: *The sponsor provided sufficient information to demonstrate that the use of the automation system is acceptable for both the screening and confirmatory ADA assays. ADA-positive and ADA-negative samples have the same results in both assays and there are no significant differences in the CV% of the mean counts for all the samples using the manual or the automated analysis.*

Neutralizing Antibody Assay

During product development, the sponsor was advised to develop a cell-based neutralizing antibody (NAb) assay or to provide a justification to support the adequacy of a competitive ligand binding assay to detect NAbs. During a type C meeting, on November 4, 2015, the Agency and the sponsor discussed the capabilities of the competitive ligand binding and the cell-based NAb assays and the Agency concluded that the sponsor provided adequate information to support the suitability of the binding assay to measure NAbs, pending review of the assay validation. Refer to the corresponding meeting minutes (DARRTS, November 4, 2015) and Haoheng Yan's review uploaded in DARRTS on November 5, 2015.

The competitive ligand binding assay is an ECL-based immunoassay. The sponsor uses a neutralizing mouse anti-dupilumab (REGN 2266) as the positive control, biotinylated REGN668 (Bio-REGN668) as the capture reagent, and Ru-labeled IL-4Rα (Ru-REGN560) as the detection reagent. The sponsor also uses a human anti-IL-4Rα monoclonal antibody (REGN675) to mitigate any potential circulating target interference in the assay by binding to free IL-4Rα present in patient serum. Serum samples are pre-treated with acid to dissociate NAb-dupilumab complexes. After dissociation, the samples are neutralized with a Tris-base solution that contains Bio-REGN668 and the anti-IL-4Rα MAb (REGN675). Bio-REGN668 is captured on an avidin-coated microplate. Ru-REGN560 is then added to the plate. In absence of NAbs, Ru-REGN560 binds to Bio-REGN668 and it is quantified using ECL. When NAbs are present, the NAbs bind to Bio-REGN668 preventing the formation of the Bio-REGN668:Ru-REGN560 complex and causing a reduction of the ECL signal. The ECL signal is inversely proportional to the concentration of NAb in the sample.

Frederick Mills reviewed the draft QC version of the validation report regn668-av-13112 (review uploaded in DARRTS on January 5, 2016) and concluded that the "assay is generally acceptable, with a sensitivity of 135-140 ng/mL, and a cutpoint requiring 22% inhibition of REGN688 MAb to its target IL4 receptor, consistent with industry practice and Guidance" and that "the sponsor has demonstrated adequate linearity of response, precision, robustness, and ruggedness."

As part of his review, Frederick Mills had three recommendations for the sponsor. Following are the recommendations (*italics black font*), the new information provided by the sponsor to address them (black font) and my evaluation of the responses (*italics blue font*).

1. *You have calculated Drug Tolerance Limits (DTL) for the REG2266 monoclonal and the REGN2339 polyclonal controls as 276 ng/mL and 498 ng/mL, respectively, where these values correspond to approximately 3 fold reductions in inhibition relative to no added REGN668 controls, and thus data acquired at these REGN668 concentrations will not accurately represent neutralizing antibody (Nab) activity in serum samples. Therefore, we recommend that you instead set Drug Tolerance Limits where the inhibition vs. REGN668 curves are slowly varying, and thus allow for more accurate measurement of*

Nab level. Furthermore, because some subjects may have low but detectable Nab levels, we recommend that you evaluate DTL at positive control levels lower than 500 ng/mL.

According to the updated validation report, the sponsor determined the drug tolerance level in neat serum in presence of 250 ng/mL of REGN2266 as 176 ng/mL.

Table 34: Drug Tolerance – Mouse Monoclonal Antibody Control (250 ng/mL of REGN2266)

REGN668 Concentration in Neat Serum (ng/mL)	250 ng/mL REGN2266			
	Set 1		Set 2	
	Mean Counts[a]	%Inhibition	Mean Counts	%Inhibition
300	2231	3	2208	4
250	2154	6	2110	8
200	1893	17	1833	20
150	1661	28	1677	27
100	1492	35	1466	36
50	1333	42	1348	41
25	1371	40	1271	45
0	1292	44	1248	46
DTL (ng/mL)	173		179	
Mean DTL (ng/mL)[b]	176			
NQC Mean Counts	2291			
Cut point	22%[c]			

a - All values listed under Mean Counts, %Inhibition, NQC Mean Counts, and DTL were calculated by SoftMax Pro software (File 160119_REGN668_Dev.sdax found in NB# 13383-143 to 13383-146).
b - Mean DTL was calculated by Excel 2010.
c - This development exercise used the validation cut point of 22%.

Reviewer's comment: *The drug tolerance determined for both 500 and 250 ng/mL of REGN2266 is significantly lower than the dupilumab trough levels measured in study r668-ad-1224 of 74 µg/mL for the biweekly treatment and 188 µg/mL for the weekly treatment. Therefore, the sponsor has not provided adequate information to confirm that the assay can appropriately detect NAbs at the measured serum drug levels. The following IR was sent on September 20, 2016:*

Regarding the neutralizing antibody assay, according to report regn668-av-13112-va-01v1, you determined the drug tolerance level in neat serum in presence of 250 ng/mL of REGN2266 as 176 ng/mL. According to the proposed package insert included in section 1.14.1.3, (b) (4) *Provide a justification why the assay drug tolerance reported is appropriate for the levels of on board drug expected in the clinical samples.*

In BLA amendment 0011 submitted September 30, 2016, the sponsor indicates that 55% of the NAb positive cases corresponded to samples with low ADA titers (from 30 to 240) and 19% of

the NAb positive cases corresponded to samples with very low ADA titers (from 30 to 60). The sponsor highlights a case when NAbs were detected in a sample with an ADA titer of 30 and a serum dupilumab concentration of 90,600 ng/mL, which is above the mean steady state trough serum concentration of 74 µg/mL. It is important to note that the sponsor uses different units in this statement, and that the serum concentration is higher but of the same order as the trough concentration.

Reviewer's comment: *The NAb determination is qualitative and not quantitative. Fred Mills requested a different evaluation of DTL for a more accurate measurement of NAb level. However, there is no titering and the results are either "positive" or "negative". The DTL is established at the concentration of drug that causes an inhibition of the same degree as the cut point (22%). Yow-Ming Wang (clinical pharmacology team leader) indicated that they are not especially concerned about the inadequate drug tolerance of the NAb assay because the PK assay can detect drug in serum, so the effect of NAbs causing reduction of drug in circulation would be detected by the PK assay. Therefore, no additional information will be requested at this time regarding the NAb assay drug tolerance.*

2. (b) (4)

Reviewer's comment: (b) (4)

To address the LDL comment, the sponsor tested 20 additional high LDL samples in presence or absence of 170 ng/mL of the antibody control, REGN2266. In presence of REGN2266 all 20 samples had a %inhibition greater than the cut point. In absence of REGN2266, all 20 samples had a %inhibition below the cut point. According to the sponsor, the results demonstrate that high levels of LDL do not seem to generate a false positive signal or interfere with the detection of NAbs at the LQC level (17 ng/mL).

Table 35: Recovery – High LDL individuals with or without REGN2266

			0 ng/mL REGN2266 (nominal)			17 ng/mL REGN2266 (nominal)		
Sample	**Sex**	**LDL (mg/dL)[a]**	**Mean Counts[b]**	**CV% Counts**	**%Inhibition**	**Mean Counts**	**CV% Counts**	**%Inhibition**
01	**Female**	**199**	2621	0	0	1838	1	30
02	**Female**	**161**	2376	1	9	1758	1	33
03	**Female**	**143**	2151	1	18	1606	4	39
04	**Female**	**209**	2773	4	-6	1885	2	28
05	**Male**	**185**	2559	1	2	1860	3	29
06	**Male**	**164.6**	2568	1	2	1830	1	30
07	**Female**	**142.4**	2626	0	0	1873	5	29
08	**Female**	**130.4**	2493	1	5	1757	4	33
09	**Male**	**146.4**	2403	4	8	1705	7	35
10	**Female**	**157**	2456	5	6	1661	1	37
11	**Female**	**139.6**	2306	2	12	1614	2	38
12	**Male**	**133**	2740	2	-5	1789	3	32
13	**Male**	**129.2**	2242	5	14	1617	1	38
14	**Male**	**147**	2405	0	8	1622	3	38
15	**Male**	**142**	2476	3	6	1806	2	31
16	**Female**	**136.6**	2599	2	1	1737	6	34
17	**Male**	**176**	2455	6	6	1640	4	37
18	**Male**	**209.6**	2532	2	3	1671	4	36
19	**Male**	**221.2**	2349	0	10	1616	1	38
20	**Female**	**180.6**	2577	0	2	1785	1	32
NQC Mean Counts			2622					
Cut Point			22%[c]					

a - LDL (mg/dL) values were provided by (b) (4)
b - All values listed under Mean Counts, CV% Counts, %Inhibition and NQC Mean Counts were calculated by SoftMax Pro software (File 160208_REGN668_Dev.sdax found in NB# 13383-149).
c - This development exercise was performed post validation and used the validation cut point of 22%.

Reviewer's comment: *During the new study there were no false positive results in the not-spiked samples. Therefore, out of 30 samples tested, only two gave false positive results. Because treatment is not discontinued due to the presence of NAbs, a 7% incidence of false positive results in high LDL samples does not constitute a safety concern.*
The additional information also supports the sponsor's claim that high levels of LDL do not interfere with the detection of NAbs at the LQC level because all the spiked samples had %inhibition results clearly above the cut point, this includes both the original and the new information, for a total of 30 samples.

3. *You have assessed analyte stability by studying the effect of accelerated stress conditions, long-term and short-term storage on the performance of the positive control (anti-REGN668 monoclonal antibody; REGN2266) in the assay. The assay controls appear to be unaffected by overnight 4°C and 4 hour room temperature (RT) storage. However, the background from the negative controls increased to 6% inhibition after 10 freeze-thaw (F/T) cycles, and we recommend that you reduce the number of F/T cycles that are*

allowed for these samples to yield inhibitions in the range seen for inter-assay precision (i.e., 4%).

Reviewer's comment: *The sponsor did not address this recommendation and the validation summary still indicates that the analyte is stable for up to 10 freeze-thaws. The following IR was sent to the sponsor on September 20, 2016 to request the results of intermediate FT cycles, if available.*

> *In table 14 of report regn668-av-13112-01v1 (Validation of a Competitive Ligand Binding Assay for Detection of Neutralizing Anti-REGN668 (Dupilumab) Antibodies in Human Serum), you provide the results of the freeze-thaw (FT) evaluation of the analyte stability. The background from the negative controls was 6% inhibition after 10 FT cycles. However, during the determination of inter-assay precision, the negative quality control (NQC) binding inhibition was determined to be 4%. To evaluate if the number of FT cycles has a gradual effect on the NQC binding inhibition and determine if the binding inhibition after 10 FT cycles is too high, submit the NQC binding inhibition results of the intermediate FT cycles.*

In BLA amendment 0011 submitted September 30, 2016, the sponsor indicated that the analysis was conducted only after completion of 10 FT cycles. In addition, the 6% inhibition is below the assay cut point (22%) and within the variability of the inhibition for the NQC during the determination of intermediate precision (range: 0-8%, mean: 4%; Table 9 in the report).

Reviewer's comment: *Because the results corresponding to fewer FT cycles are not available, it is not possible to determine if there are trends in the inhibition that may correlate with the number of FT cycles. However, based on the results corresponding to testing of the NQC samples during assay validation, the inhibition after 10 FT cycles appears to be within the assay variability. Therefore the sponsor provided sufficient information to support the stability of the NQC after 10 FT cycles.*

In addition, the sponsor provided the results corresponding to the long-term stability study for REGN2266. The QCs were stored at either -20°C or -80°C and tested after 3, 6, 10, 12, 18, 21, and 24 months.

Reviewer's comment: *In all cases, the results for the negative controls were below the cut point and the results for the positive controls were above the cut point. In addition, the %inhibition was the highest for the HQC, and higher for the MQC than for the LQC. Therefore, the information confirms that the QCs are stable for up to 24 months at -20°C and -80°C.*

III. Signatures:

Printed Name:	Electronic Signature:
Cristina Ausin-Moreno OPQ/OBP/DBRR IV	
Michele Dougherty OND/TBBS (formerly OPQ/OBP/ DBRR IV	

U.S. FOOD & DRUG ADMINISTRATION

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

Date: 02/09/2016

To: Administrative File, STN 761055/0

From: Maria Jose Lopez Barragan, PhD., Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Reyes Candau-Chacon, PhD., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV

Subject: New Biologic License Application (BLA)

US License: 1760

Applicant: Regeneron Pharmaceuticals, Inc.

Facilities: Regeneron Pharmaceuticals, Inc., 81 Columbia Turnpike, Rensselaer, NY
FEI: 1000514603 (DS manufacture)

Product: Dupixent® (dupilumab); REGN668

Dosage: Sterile solution for subcutaneous injection (150 mg/mL)

Indication: Treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, (b) (4) , or (b) (4) not advisable.

Goal date: 03/29/2017

Recommendation for approvability: This BLA is recommended for approval from a microbiology product quality perspective.

Review Summary

Regeneron Pharmaceuticals, Inc. has submitted BLA STN 761055 to obtain approval of dupilumab (Regeneron company code: REGN668). Dupilumab is also referred to as SAR231893 (Sanofi company code). Dupilumab is a recombinant human IgG4 monoclonal antibody that binds specifically to the IL-4R alpha sub-unit of the IL-4 and IL-13 receptor complex.

BLA 761055 was submitted in eCTD format as a rolling BLA. The original application was submitted on 03/31/2016 and contained incomplete modules 1, 2, 4 and 5. Incomplete module 3 was submitted on 06/29/2016 (eCTD 0003) with additional quality information submitted on 07/29/2016 (eCTD 0004). This review contains the assessment of the manufacturing process for dupilumab drug substance from a microbial perspective. The microbiology review of dupilumab DP was performed by Dr. Lakshmi Rani Narasimhan.

Drug Substance Quality Microbiology Information Reviewed

Description	eCTD Sequence	Date
Original BLA	0003	06/29/2016
Original BLA	0004	07/29/2016
Response to information request	0025	12/05/2016
Response to information request	0037	01/25/2017

3.2.S DRUG SUBSTANCE

S.1 GENERAL INFORMATION

Dupilumab is a human IgG monoclonal antibody, anti-(human interleukin 4 receptor α) (human REGN668 heavy chain), disulfide with human REGN668 κ-chain, dimer. Dupilumab is produced in CHO cells.

The description is satisfactory

S.2 Manufacture

S.2.1 Manufacture(s)

The following facilities are involved in the manufacture and in-process and release testing (for microbial attributes) of dupilumab drug substance (b) (4):

Site	Responsibilities
Regeneron Pharmaceuticals, Inc. 81 Columbia Turnpike, Rensselaer, NY 12144-3411 (USA) FEI: 1000514603	• Manufacture and control of dupilumab DS (b) (4) • Bioburden and endotoxin in-process and DS (b) (4) release testing

Dupilumab DS is manufactured in (b) (4)

Reviewer's comment: a pre-license inspection (PLI) was conducted at the dupilumab drug substance manufacturing facility from October 31st through November 4th 2016 (see under FACTS assignment 11683525).

Satisfactory

S.2.2 Description of Manufacturing Process and Process Controls: Drug Substance

S.2.2.1 Batch and Scale Definition

(b) (4)

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

Satisfactory

Conclusion

I. The Drug Substance section of this BLA was reviewed from a microbial control and microbiology product quality perspective and it is recommended for approval.

II. Non-microbial information and data from the Drug Substance section of this BLA should be also reviewed by OBP.

III. A pre-license inspection (FACTS assignment 11683525) was conducted at Regeneron Pharmaceuticals, Inc., Rensselaer, NY, from October 31st through November 4th 2016 by CDER/OPQ: OPF/DMA/BIV (María José López Barragán), OBP/DBRRIV (Gunther Boekhoudt) and OPF/DIA/IABI (Wayne Seifert).

FDA Information Request for BLA STN 761055/0 (Dupilumab Drug Substance) submitted on 11/30/2016. Sponsor responses in Amendment 0025 dated 12/05/2016

FDA Information Request for BLA STN 761055/0 (Dupilumab Drug Substance) submitted on 1/18/2017. Sponsor responses in Amendment 0037 dated 1/25/2017

Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 2/10/2017 08:42:40AM
GUID: 508da7160002977f7ca389c8f849b707

U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: February 06, 2017
To: Administrative File, BLA 761055/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA) Review memo
US License: #1760
Applicant: Regeneron Pharmaceuticals Inc.
Facility: Sanofi Winthrop Le Trait, 1051 Boulevard, 76580 Industriel Le Trait, France (FEI # 3003259844) - Pre-filled syringe (PFS)
Product: Dupilumab (dupixent)
Dosage: Sterile, preservative-free liquid formulation in a single-use pre-filled syringe (PFS) with a safety system (PFS-S), containing 2mL of 150 mg /mL for subcutaneous injection.
Indication: For the treatment of atopic dermatitis
Due Date: March 29, 2017.

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended from a product quality microbiology and sterility assurance perspective for approval with the following post-marketing commitments (PMC):

1. Revise the (b) (4) CFU/(b) (4)mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches have been analyzed.
2. Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL drug product. Submit the data in the first annual report.

SUMMARY:

Regeneron Pharmaceuticals Inc. submitted a new biologics license application, BLA 761055 to license dupilumab for the treatment of atopic dermatitis. Drug substance is manufactured by Regeneron Pharmaceuticals, Inc., and the drug product in pre-filled syringe is manufactured at Sanofi Winthrop, Le Trait, France.

The rolling submission was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, Module 2 and Module 3. Module 3 includes appendices and a regional section (3.2.R). Sequence 0003 containing Module 3 was submitted on June 29, 2016. Sequence 0004 containing additional information Module 3 was submitted on July 29, 2016. Letter of authorization (LOA) for (b) (4) Type III DMF (b) (4) to review the (b) (4) and LOAs for (b) (4), Type V DMF (b) (4) to review (b) (4) and (b) (4)

Type V DMF (b) (4) to review the (b) (4) were provided.

INTRODUCTION

Dupilumab drug product (DP) is manufactured by (b) (4) from Dupilumab drug substance (DS) at Sanofi Winthrop, Le Trait, France. This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0003	April 05, 2015	Original
0004	June 29, 2016	Original
0013	October 24, 2016	Amendment
0019	November 14, 2016	Amendment
0021	November 23, 2016	Amendment
0030	January 04, 2016	Amendment
0031	January 06, 2016	Amendment

ASSESSMENTS:

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product- Pre-Filled Syringe

The drug product (DP) is a sterile, clear to slightly opalescent, colorless to pale yellow, (b) (4) solution with pH 5.9. DP is presented in a single use prefilled syringe (PFS), containing 2 mL of 150 mg/mL DP for subcutaneous (SC) injection. The nominal composition of the DP presented in Table 1 is reproduced below.

Table 1: Nominal Composition of Dupilumab Solution for Injection

Component	Function	Reference to Quality Standard	Drug Product Nominal Composition	Nominal Amount per Prefilled Syringe (mg)[a]
Dupilumab	Active pharmaceutical ingredient	Custom specification	150 mg/mL	300
L-Histidine (b) (4)	(b) (4)	USP, Ph. Eur., JP	20 mM	6.2[b]
		Ph. Eur., JP		
L-Arginine (b) (4) hydrochloride		USP, Ph. Eur., JP	25 mM	(b) (4)
Sodium Acetate (b) (4)		USP, Ph. Eur., JP	12.5 mM	
(b) (4)		USP, Ph. Eur., JP		
Sucrose		NF, Ph. Eur., JP	5% (w/v)	100
Polysorbate 80		NF, Ph. Eur., JP	0.2% (w/v)	4
Water for Injection		USP, Ph. Eur.		(b) (4)

[a] Based on a 2.0 mL injection volume

[b] Reported as milligrams histidine base (MW = 155.16 g/mol), calculated assuming a molar concentration of 20 mM histidine

(b) (4)

USP, United States Pharmacopeia; NF, National Formulary; Ph. Eur., European Pharmacopeia; JP, Japanese Pharmacopeia

Satisfactory

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

(b) (4)

Satisfactory

Conclusion

I. The drug product section of this BLA, as amended, is recommended from a product quality microbiology and sterility assurance perspective for approval with the following post-marketing commitments (PMC):

1. Revise the (b) (4) CFU (b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches havebeen analyzed.
2. Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data

from one additional batch of 150 mg/mL dupilumab drug product. Submit the data in the first annual report.

II. Product quality aspects other than microbiology should be reviewed by the OBP reviewer.

III. See Panorama for the compliance status of the drug product manufacturing site, Sanofi Winthrop Le Trait, Le Trait, France.

The following information requests sent out during the review cycle were satisfactorily addressed by the Sponsor

October 17, 2016

I. Container closure integrity test

1. Please clarify and confirm if the PFS used for the CCI test qualification (b) (4) are the same as the commercial PFS described in 3.2.P.7.
2. Please submit the following information regarding correlating study performed at (b) (4) for microbial ingress and dye ingress method for CCI testing:

a. Description of the microbial ingress test including critical parameters (initial and final concentration of challenge organism, pressure /vacuum challenge and time of exposure of sample units to the challenge), number of positive, negative controls and test units used in the study, preparation of positive and negative control.

b. Description of the test including critical parameters (concentration of dye, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge and dye), drug product lots used and number of positive, negative controls and test units used in the study, preparation of positive and negative controls.

II. Drug product manufacturing process

1. (b) (4)

2. (b) (4) Please update section P.3.3 with this information.

III. Process Validation

(b) (4)

(b) (4)

Shipping

1. Please provide the following information regarding the simulated shipping validation performed as per ASTM D4169-9.

   PFS (QUA-BD-2015-22437)

   a. Indicate the number of product-filled syringes which were tested for endotoxin and sterility.
   b. Indicate the number of media-filled syringes which were tested for sterility.
   c. Please provide the simulated shipping conditions that were used for the plunger movement study which was performed to demonstrate that the sterility of drug product will not be compromised during air transportation.

   PFS-S (QUA-BD-2015-22452)

   a. Indicate the number of product-filled syringes which were tested for endotoxin and sterility.
   b. Indicate the number of media-filled syringes which were tested for sterility.
2. Please clarify if a real time shipping validation PFS and PFS-S has been completed and submit the information and summary data if real time shipping validation has been completed.

IV. Analytical procedures

Sterility

(b) (4)

V. Validation of Analytical procedures

Bioburden

The bioburden qualification study was performed with only two batches of dupilumab DP. As a post-marketing commitment, qualification data from one additional batch of 150 mg/mL DP should be provided in the first annual report.

Sterility

The sterility qualification study was performed with only two batches of dupilumab DP. As a post-marketing commitment, qualification data from one additional batch of 150 mg/mL DP should be provided in the first annual report.

November 16, 2016

FDA comments on firm's response submitted in Sequence # 0013:

I. Container closure integrity test

1. As per section 3.2.P.7, the commercial dupilumab PFS are 2.25 mL (b) (4) syringes but in Regeneron's AQ- SR-7899 "Determination of Container Closure Integrity by Dye Ingress Method for REGN668" (b) (4) mL PFS are used for the qualification. Please clarify and confirm if commercial 2.25 mL (b) (4) syringes are used for CCI test method qualification at Regeneron.

2. Please clarify if the system suitability control uses a small breach size, (b) (4) µm for the routine dye ingress CCI test of dupilumab PFS at (b) (4). Please implement the use of control with (b) (4) µm breach size if it is not currently used during routine CCI testing.

II. Process Validation

(b) (4)

December 22, 2016

FDA comments on firm's response submitted in Sequence # 0021:

We acknowledge your plan of manufacturing additional batches to support (b) (4) is not recommended. (b) (4) Update Table 6, Comparison of validation and production parameters in section 3.2.P.3.5, accordingly

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: March 07, 2017
To: Administrative File, STN 761055/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Qiu, Zhihao Peter, Ph.D., Branch 1 Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 761055
Applicant: Regeneron Pharmaceuticals, Inc.
Mfg Facility: Drug Substance: Regeneron Pharmaceuticals, Inc. (FEI: 1000514603)
Drug Product: Sanofi Winthrop Industrie (FEI: 3003259844)
Product: Dupilumab (Dupixent)
Dosage: Vial, 150 mg/ml, Subcutaneous Injection
Indication: Treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, [(b) (4)], or [(b) (4)] not advisable.
Due Date: March 29, 2017

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes manufacture of Dupilumab DS at the Regeneron Pharmaceuticals, Inc. (FEI: 1000514603) facility in Rensselaer, New York, and DP at the Sanofi Winthrop Industrie (FEI: 3003258844) facility in Le Trait, France. Both locations are multi-product manufacturing facilities. The final dosage form consists of a ready to use, sterile, single dose, prefilled and disposable [(b) (4)] Type 1, 2.25 ml glass syringe with 27 G ½ [(b) (4)] needle. The container closure system includes an [(b) (4)] needle shield is assembled with an [(b) (4)] plunger stopper within a safety system preassembled with finger flange.

Dupilumab (IgG4 isotype) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. Each heavy chain contains a serine-to-proline mutation at amino acid 233, which is located in the hinge region of the Fc domain, to reduce the propensity of the antibody to form half-antibodies in solution. There is a single N-linked glycosylation site (Asn302) in each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. The antibody, based on the

primary sequence (in the absence of N-linked glycosylation), possesses a molecular weight of 146,897.0 Da, taking into account the formation of 16 disulfide bonds and removal of Lys452 from each heavy chain C-terminus. The variable domains of the heavy and light chains combine to form complementarity-determining regions (CDRs) for the binding of Dupilumab to its target, interleukin-4 receptor alpha (IL-4Rα).

Dupilumab is produced [redacted] with recombinant Chinese hamster ovary (CHO) cells [redacted] The facilities performing manufacture, testing, release and storage of Dupilumab (Dupixent) DS and DP are identified within Table 1 and 3.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

The proposed Dupilumab DS Manufacturers, Testing and Storage Facilities are provided in Table 1.

TABLE 1: Manufacturers for Dupilumab DS

Site Name	Address	FEI #	Responsibility
Regeneron Pharmaceuticals, Inc.	81 Columbia Turnpike Rensselaer, NY 12144-3411	1000514603	Manufacture and control 1) Dupilumab DS [redacted]; 2) All DS [redacted] in-process testing [redacted], in-vitro test for adventitious viruses, [redacted] 3) DS, [redacted] bulk PFS, PFS-S and PFS release and stability testing; and 4) Final release site for PFS-S and PFS for distribution.
Regeneron Pharmaceuticals, Inc.	26 Tech Valley Drive East Greenbush 12061	1000514603	[redacted]
[redacted]			DS [redacted] in-process and release analytical testing.
			DS, [redacted] PFS, PFS-S and PFS release and

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(b) (4)

CONCLUSION

Adequate descriptions were provided for the facilities proposed for Dupilumab (Dupixent) DS and DP manufacture. The subject BLA is recommended for approval from a facilities assessment perspective.

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