CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761033Orig1s000

CHEMISTRY REVIEW(S)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Application BLA 761033

Submission Type: Standard

Established/Proper Name: reslizumab (CEP-38072)

Applicant:

Teva Branded Pharmaceuticals

Letter Date: March 28, 2015

Chemical Type:

Original BLA

Stamp Date: March 30, 2015

Strength: 100mg/10 mL

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

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	X	☐	
2.	Botanical[1]	☐	X	
3.	Naturally-derived Product	☐	X	
4.	Narrow Therapeutic Index Drug	☐	X	
5.	PET Drug	☐	X	
6.	PEPFAR Drug	☐	X	
7.	Sterile Drug Product	X	☐	
8.	Transdermal[1]	☐	X	
9.	Pediatric form/dose[1]	☐	X	
10.	Locally acting drug[1]	☐	X	
11.	Lyophilized product[1]	☐	X	
12.	First generic[1]	☐	X	
13.	Solid dispersion product[1]	☐	X	
14.	Oral disintegrating tablet[1]	☐	X	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
15.	Modified release product[1]		☐	X	
16.	Liposome product[1]		☐	X	
17.	Biosimiliar product[1]		☐	X	
18.	Combination Product _____		☐	X	
19.	Other_____		☐	☐	
	Regulatory Considerations				
20.	USAN Name Assigned		X	☐	reslizumab
21.	End of Phase II/Pre-NDA Agreements		X	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	X	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	X	
24.	Comparability Protocol(s)[2]		X	☐	
25.	Other_____		☐	☐	
	Quality Considerations				
26.	Drug Substance Overage		☐	X	
27.	Design Space	Formulation	☐	X	
28.		Process	☐	X	
29.		Analytical Methods	☐	X	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	X	
32.	Parametric Release in lieu of Sterility Testing		☐	X	
33.	Alternative Microbiological Test Methods		☐	X	
34.	Process Analytical Technology[1]		☐	X	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	X	☐	
36.		Excipients	X	☐	All excipients except sucrose are tested using compendial methods. A [redacted] (b) (4) method is used for testing of sucrose. Method validarion report was provided
37.		Microbial	☐	X	
38.	Unique analytical methodology[1]		☐	X	
39.	Excipients of Human or Animal Origin		☐	X	
40.	Novel Excipients		☐	X	
41.	Nanomaterials[1]		☐	X	
42.	Hold Times Exceeding 30 Days		☐	X	
43.	Genotoxic Impurities or Structural Alerts		☐	X	
44.	Continuous Manufacturing		☐	X	
45.	Other unique manufacturing process[1]		☐	X	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	X	
47.	New delivery system or dosage form[1]		☐	X	
48.	Novel BE study designs		☐	X	
49.	New product design[1]		☐	X	
50.	Other_____		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	X	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	X	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided?	X X	☐	☐	The 356h form states that all manufacturing & testing sites are ready for inspection. Manufacturing schedule provided in cover letter.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	❑ Is the schedule feasible to conduct an inspection within the review cycle?	X			
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	X	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	X	☐	☐	
DRUG PRODUCT INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION	X	☐	☐	
BIOPHARMACEUTICS					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	X	This is a biological product. This is the purview of the Office of Clinical Pharmacology
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	X	☐	☐	The clinical drug product is manufactured by the proposed commercial process
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	X	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	X	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☐	X	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk	X	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			X	

Maria Teresa Gutierrez Lugo -S

Digitally signed by Maria Teresa Gutierrez Lugo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S
Date: 2016.02.29 10:50:30 -05'00'

First approval for indication

Recommendation: Approval

BLA 761033
Addendum 1
February 11, 2015

Drug Name/Dosage Form	Cinqair/injection
Strength/Potency	100 mg/10 ml (10 mg/ml)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Proposed Indication	To reduce exacerbations, relieve symptoms and improve lung function in adults with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.
Applicant/Sponsor	Teva Pharmaceuticals

Name and Title	Signature and Date
Maria-Teresa Gutierrez-Lugo, Ph.D. Application Technical Lead Division of Biotechnology Research and Review III Office of Biotechnology Products	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S Date: 2016.02.23 10:29:47 -05'00'
Susan Kirshner, PhD Division of Biotechnology Research and Review III Office of Biotechnology Products	For Susan Kirshner Howard A. Anderson -S Digitally signed by Howard A. Anderson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605528, cn=Howard A. Anderson -S Date: 2016.02.23 11:13:33 -05'00'

1. INSPECTIONAL ACTIVITIES FOR THE DRUG SUBSTANCE AND DRUG PRODUCT MANUFACTURING FACILITIES

A pre-license inspection of the drug substance manufacturing facility (b) (4) was conducted (b) (4) following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, under FACTS assignment # (b) (4). The inspection covered drug substance manufacturing areas (b) (4) and warehouse (b) (4) and an offsite warehouse (b) (4). The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products; CP 7346.832, Pre-Approval Inspections/Investigations; and ICH Q7. This inspection was limited to the manufacturing of reslizumab. A seven-item 483 was issued. The recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived.

2. SUMMARY OF PRIMARY QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of STN 761033 for Cinqair (reslizumab). The data submitted in the Biologics License Application support the conclusion that the manufacture of Cinqair (reslizumab) is well controlled and leads to a product that is pure and potent. The reslizumab drug substance and drug product is free from endogenous and adventitious agents sufficient to meet the parameters recommended by the FDA. The conditions used for manufacturing reslizumab drug substance and drug product have been sufficiently validated, and consistent product has been manufactured from the multiple production runs. The Office of Biotechnology Products recommends Cinqair (reslizumab) be approved for human use (under conditions specified in the package insert).

The Office of Biotechnology Products recommends an expiry period of 36 months for reslizumab drug substance and drug product when stored at recommended storage conditions of 2-8°C.

II. List Of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirement: Refer to the approval letter

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review: Refer to Review by Dr. Jibril Abdus-Samad

VII. Review Of Immunogenicity Assays – Module 5.3.1.4: Refer to review by Dr. Joao Pedras-Vasconcelos

First approval for indication

Recommendation: Approval

BLA 761033
Review 1
February 11, 2015

Drug Name/Dosage Form	Cinqair/injection
Strength/Potency	100 mg/10 ml (10 mg/ml)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Proposed Indication	To reduce exacerbations, relieve symptoms and improve lung function in adults with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.
Applicant/Sponsor	Teva Pharmaceuticals

a. Names

i.	Proprietary Name:	Cinqair
ii.	Trade Name:	Cinqair
iii.	Non-Proprietary/USAN:	reslizumab
iv.	CAS name:	241473-69-8
v.	Common name:	CEP-38072
vi.	INN Name:	reslizumab
vii.	OBP systematic name:	MAB HUMANIZED (IGG4) (b) (4) (IL5_HUMAN) CEP38072]
viii.	Other Names:	CEP-38072, CTx55700, SCH 55700

b. Pharmacology category: anti-interleukin 5 monoclonal antibody

Product Overview

Cinqair (reslizumab) is a humanized IgG4, kappa anti-IL5 monoclonal antibody produced in NS0 cells. Reslizumab contains the complementary determining regions (CDRs) of the original rat anti-human antibody 39D10 grafted onto a human framework. Reslizumab is glycosylated at the Fc region. The N-linked oligosaccharides of reslizumab are (b) (4) derived from NS0 cell lines. The predicted molecular mass is 146.8 kDa. Reslizumab binds to and neutralizes human IL-5. IL-5 mediates the proliferation, activation, and survival of target eosinophil cells. The mechanism of action for reslizumab is achieved by blocking IL-5 binding to its specific receptor.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/ DIVISION
Drug Substance	Ramesh Potla	Division of Biotechnology Review and Research III
Drug Product	Tracy Denison	Division of Biotechnology Review and Research III
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	Lakshmi Narasimhan	Division of Microbiology Assessment
Facilities	Nguyen, Thuy	Division of Inspectional Assessment
Immunogenicity*	Joao Pedras-Vasconcelos	Division of Biotechnology Review and Research III
Immunogenicity*	Amy Rosenberg	Division of Biotechnology Review and Research III
Immunogenicity*	Susan Kirshner	Division of Biotechnology Review and Research III
Drug substance and Drug Product Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment
Business Regulatory Project Manager	Andrew Shiber	OPRO
Application Technical Lead	Maria-Teresa Gutierrez-Lugo	Division of Biotechnology Review and Research III
Tertiary Reviewer	Susan Kirshner	Division of Biotechnology Review and Research III

* The immunogenicity review is filed as a separate memo

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Colette Jackson	ODEII/DPARP
Cross-disciplinary Team lead	Banu Karimi-Shah	ODEII/DPARP
Clinical Reviewer	Kathleen Donohue	ODEII/DPARP
Pharm/Tox	Carol Galvis, Marcie Wood	ODEII/DPARP
Clinical Pharmacology	Yunzao Ren, Ping Ji	OCP
Statistics	Lan Zeng	OB/DBIV

Quality Review Team - Signature Page

DISCIPLINE	REVIEWER	BRANCH/ DIVISION	e-Signature
Drug Substance	Ramesh Potla	Division of Biotechnology Review and Research III	Ramesh B. Potla -S Digitally signed by Ramesh B. Potla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=001210 1865, cn=Ramesh B. Potla -S Date: 2016.02.18 11:15:45 -05'00'
Drug Product	Tracy Denison	Division of Biotechnology Review and Research III	Tracy A. Denison -S Digitally signed by Tracy A. Denison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=200115 4781, cn=Tracy A. Denison -S Date: 2016.02.19 15:52:14 -05'00'
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment	Bo Chi -S Digitally signed by Bo Chi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bo Chi -S, 0.9.2342.19200300.100.1.1=1300194 820 Date: 2016.02.22 13:32:56 -05'00'
Microbiology Drug Product	Lakshmi Narasimhan	Division of Microbiology Assessment	Lakshmi Narasimhan -S Digitally signed by Lakshmi Narasimhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640 223, cn=Lakshmi Narasimhan -S Date: 2016.02.18 13:02:22 -05'00'
Facilities	Nguyen, Thuy	Division of Inspectional Assessment	Thuy T. Nguyen -S Digitally signed by Thuy T. Nguyen -S DN: c=US, o=U.S.Government, ou=HHS, ou=FDA, ou=People, cn=Thuy T. Nguyen -S, 0.9.2342.19200300.100.1.1=200042563 9 Date: 2016.02 22 13:10:13 -05'00'
DS and DP Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroost -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300 096547, cn=Patricia F. Hughestroost -S Date: 2016.02.18 12:59:16 -05'00'
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.02.23 07:35:31 -05'00'

Application Technical Lead	Maria-Teresa Gutierrez-Lugo	Division of Biotechnology Review and Research III	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S Date: 2016.02.18 10:48:12 -05'00'
Tertiary Reviewer	Susan Kirshner	Division of Biotechnology Review and Research III	Susan L. Kirshner -S Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300194629, cn=Susan L. Kirshner -S Date: 2016.02.19 15:56:54 -05'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS

A. Submissions reviewed

Submission	Date Received	Review Completed (Yes/No)
Original submission	March 30, 2015	Yes
STN 761033/3	May 22, 2015	Yes
STN 761033/9	August 7, 2015	Yes
STN 761033/13	September 11, 2015	Yes
STN 761033/14	September 11, 2015	Yes
STN 761033/17	September 30, 2015	Yes
STN 761033/20	October 9, 2015	Yes
STN 761033/24	October 30, 2015	Yes
STN 761033/25	November 5, 2015	Yes
STN 761033/26	November 9, 2015	Yes
STN 761033/28	November 23, 2015	Yes
STN 761033/29	November 24, 2015	Yes
STN 761033/30	November 30, 2015	Yes
STN 761033/32	December 2, 2015	Yes
STN 761033/34	December 4, 2015	Yes
STN 761033/35	December 7, 2015	Yes
STN 761033/36	December 7, 2015	Yes
STN 761033/37	December 7, 2015	Yes
STN 761033/39	December 14, 2015	Yes
STN 761033/40	December 15, 2015	Yes

STN 761033/41	December 22, 2015	Yes
STN 761033/42	December 22, 2015	Yes
STN 761033/44	January 5, 2016	Yes
STN 761033/45	January 13, 2016	Yes
STN 761033/46	January 15, 2016	Yes
STN 761033/47	January 19, 2016	Yes
STN 761033/50	January 29, 2016	Yes

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS
(b) (4)	III	(b) (4)		3	Adequate	None
	III			3	Adequate	None
	V			1*	Adequate	None
	V			1	Adequate	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).

* Review of the MF focused on the media components relevant to this submission

3. CONSULTS:

None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761033 for Cinqair (reslizumab), manufactured by Teva Pharmaceuticals. The data submitted in this application are adequate to support the conclusion that the manufacture of Cinqair is well controlled and leads to a product that is pure and potent. We recommend that Cinqair be approved for human use under the conditions specified in the package insert.

a. Benefit/Risk Considerations

Cinqair (reslizumab) is an anti-interleukin 5 (anti-IL-5) monoclonal antibody intended for the treatment of asthma. The proposed dose is 3 mg/kg intravenously every four weeks. The proposed indication is to "reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids". Reslizumab is the second in the class of anti-IL-5 monoclonal antibody products. This class also includes mepolizumab, approved on November 4, 2015 as add-on maintenance treatment for patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

Asthma with eosinophilic phenotype is a serious condition associated with chronic morbidity, including frequent exacerbations. Reslizumab is intended for the treatment of asthma with eosinophilic phenotype. Review of the clinical data by OND determined that there is significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations in adults. However, evidence of efficacy and safety was less robust for subgroups with low enrollment, such as adolescents and African Americans. These findings were discussed at an advisory committee on December 9, 2015. The committee did not recommend approval of reslizumab for adolescents. Based on this, reslizumab is recommended for adults only.

An increased risk of anaphylaxis, malignancy, or creatine phosphokinase (CPK) elevations was observed in patients treated with reslizumab during the asthma clinical trials.

OND determined the following risk/benefit: A physician who treated 1,000 patients with asthma with eosinophilic phenotype with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations, but could expect to manage 3

additional cases of anaphylaxis, 3 additional cases of malignancy, and 46 additional cases of CPK elevations.

Mepolizumab is an alternative anti-IL5 monoclonal antibody with comparable efficacy and a more favorable safety and tolerability profile. It is administered subcutaneously instead of intravenously. An increased risk of anaphylaxis, malignancy, or CPK elevations was not observed in the clinical trials for mepolizumab. Reslizumab represents a modest addition to the armamentarium and may prove useful for patients who cannot tolerate mepolizumab. Due to the risk of anaphylaxis, reslizumab is not suitable for home administration. Labelling should be sufficient to address the safety concerns.

The DS manufacturing process is well controlled and should consistently deliver DS of desired quality. However, (b) (4) DS control strategy can be implemented (b) (4) and (b) (4) may be conducted post licensure as Post Marketing Commitments (PMCs) because the applicant can consistently produce reslizumab DS that is safe, pure, and potent. The implementation (b) (4) will result better control of the overall process performance and improve the long term robustness of the process. Therefore, four PMCs related to the DS are included in the approval of this application (see section B, PMCs 1 - 4).

The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. However, confirmatory information for worst case microbiology studies, method improvements are needed to corroborate findings reported in the license application. In addition, the (b) (4) fill volume content recommendations in United States Pharmacopeia (USP) General Chapter <1151>. Because information provided in the license application show that the applicant can consistently produce DP that is safe, pure, and potent the confirmatory studies and reduction of fill volume may be conducted post licensure. Therefore, four PMCs related to DP are included with the approval of this application (see section B, PMCs 5 – 8).

An additional PMC, related to both DS and DP is included with the approval of this application. This PMC is to evaluate, and if indicated revise, all the release and stability specifications after a sufficient number of lots of reslizumab are manufactured, usually around 30 lots. This is not an approvability issue because the current specifications are supported by clinical and current manufacturing experience and lead to a product that is safe, pure and potent. Revising the specifications after ~30 lots are manufactured will better reflect commercial manufacturing experience (see section B, PMCs 5 – 8).

b. Draft Action letter language

Manufacturing location:

- Drug substance – [redacted] (b) (4)
- Drug product – [redacted] (b) (4)
- Fill size and dosage form – 10 mg/ml, injection
- Dating period:
    - Drug product – 36 months; 2-8 ºC
    - Drug substance – 36 months; 2-8ºC
- Exempt from lot release

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

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

1. To improve the overall control strategy of the drug substance manufacturing process [redacted] (b) (4)
2. To implement a [redacted] (b) (4) in the drug substance manufacturing process.
3. To re-evaluate and tighten the [redacted] (b) (4) endotoxin acceptance criteria for the [redacted] (b) (4) samples after manufacturing 30 batches of reslizumab.
4. To establish a hold time limit for the intermediate [redacted] (b) (4) These hold times should be validated at scale to demonstrate that these [redacted] (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.

5. To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab.

6. To requalify the microbial retention study at routine manufacturing/room temperature and submit the results in accordance with 21 CFR 601.12 by June 2016.

7. To requalify the dye ingress CCI test method with reslizumab 10 mL/20 mm vial under worst case challenge conditions using comprised positive controls with a breach size of ≤ (b)(4) µm and submit the data in accordance with 21 CFR 601.12 by April 2016.

8. To reduce the vial overfill to comply with compendial recommendations.

9. To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from at least thirty released lots of reslizumab drug substance and drug product.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

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

CQA	Source or Origin	Risk	Control Strategy	Other
Identity	General CQA, intrinsic to the molecule. Major influencing factors include MCB/WCB genetic stability and production bioreactor.	Safety and Efficacy	Identity is tested at release (b) (4) Controls also include (b) (4)	
Potency In vitro cell-based bioassay	Intrinsic to the molecule	Directly linked to efficacy In vitro potency is a measure of reslizumab's activity in inhibiting IL-5 mediated proliferation of (b) (4) cell line	Potency is tested on release and stability.	The applicant addressed the Agency request and revised the specifications for potency to better reflect clinical and manufacturing experience.
(b) (4)	(b) (4)	Potential impact on safety not fully understood	(b) (4)	The applicant addressed the Agency request and revised the specifications (b) (4) to better reflect clinical and manufacturing experience.
		Safety and Efficacy Potential impact on		The applicant addressed the Agency request and

(b) (4)	safety and efficacy not fully understood	(b) (4)	revised the specifications (b) (4) to better reflect clinical and manufacturing experience
	Safety and Efficacy Potential impact on safety and efficacy not fully understood		
	Safety, especially immunogenicity		The applicant addressed the Agency request and revised the specifications (b) (4) to better reflect clinical and manufacturing experience
	Safety and Efficacy Potential impact on safety and efficacy not fully understood		
(b) (4)	Safety and efficacy	Not currently part of DS control strategy	A PMC was agreed upon (b) (4)

(b) (4)			(b) (4)
(b) (4)	Safety and efficacy	Not currently part of DS control strategy. (b) (4)	

B. Drug Substance: Reslizumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

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

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

CQA	Source or Origin	Risk	Control Strategy	Other
Appearance Color, clarity and visible particulate matter	General CQA Appearance might be impacted by the cell culture conditions, formulation process, but may also be an indicator of product degradation or other changes to the product.	Safety and efficacy	Appearance testing is part of DS release and stability testing. The acceptance criteria for DS at release and stability require that the DS is free of foreign particulates throughout the intended storage duration. (b) (4)	
Protein Concentration	General CQA Protein concentration (b) (4)	Safety and efficacy	The protein content of reslizumab is controlled during (b) (4) testing and is monitored as part of DS release and stability specifications.	
pH	General CQA (b) (4) pH may be impacted on stability by breaches in container closure integrity or container closure leachables and by changes in the product.	Safety and efficacy	pH is assessed during (b) (4) testing as well as part of DS release and stability testing.	
Osmolality	General CQA (b) (4)	Safety	Osmolality is tested for reslizumab DS at release and on stability.	
(b) (4)		Safety	(b) (4)	

(b) (4)		(b) (4)	
	Safety		
	Safety		
	Immunogenicity and safety		
	Immunogenicity and safety		

(b) (4)		(b) (4)	
	Immunogenicity and safety		The applicant addressed the Agency request and revised the specifications (b) (4) to better reflect clinical and manufacturing experience.
	Impact on safety (b) (4)		
	Safety		
	Safety		

B. Drug Substance Quality Summary (cont.)

1. Description

Reslizumab is a humanized IgG4, κ monoclonal antibody produced in a NS0 cell line [redacted] at [redacted] scale. The reslizumab DS manufacturing process consists of [redacted] Drug substance is [redacted] stored at 2-8 C. For additional information see Appendix A and Appendix B in the initial integrated review.

2. Mechanism of action

Reslizumab binds to soluble IL5 and blocks IL5 binding to the IL5 receptor alpha on eosinophils and other cells expressing the IL5 receptor. IL5 is a soluble dimer and is not expressed on cell surfaces. Therefore, Fc effector function is not a part of the reslizumab MOA. For additional information see Appendix A in the initial integrated review.

3. Potency Assay

Potency of reslizumab is defined as the percent activity relative to a reslizumab reference standard. The potency assay is a cell-based potency assay using [redacted] cell line, that expresses the IL-5 receptor. The biological activity of reslizumab is measured by inhibition of cell growth induced by IL-5 in a dose-dependent manner. Cell viability is measured [redacted] For additional information see Appendix A in the initial integrated review.

4. Reference material(s)

The current reference standard program for reslizumab comprises of a single reference standard, Reference Standard batch 202709ARS is used for release and stability testing.

The primary reference standard was developed from DS batch 202709 manufactured in 2011. This DS batch was manufactured by the commercial manufacturing process and it is representative of phase 3 asthma trials. Protocols for the qualification of a two-tier reference standard system were provided in the application and found appropriate. (b) (4) For additional information see Appendix A in the initial integrated review.

5. Critical starting materials or intermediates

Master Cell Bank MCB (b) (4) was derived from (b) (4) Working Cell Bank WCB (b) (4) was derived from (b) (4) MCB (b) (4) and WCB (b) (4) were properly qualified. A protocol for qualification of future cell banks was reviewed as part of the BLA and found acceptable. For additional information see Appendix A in the initial integrated review.

6. Manufacturing process summary

(b) (4)

Reslizumab is manufactured (b) (4)
Microbial quality of the DS manufacturing process is well controlled (b) (4)

The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with (b) (4) and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents. For additional information see Appendix A and Appendix B in the initial integrated review.

7. Container closure

The drug substance container closure (CCS) is [redacted] (b) (4) suitable for reslizumab manufacturing based on extractable leachable studies, and stability data. These data support that CCS is safe for use, maintain integrity during shipping, and prevent leaching. For additional information see Appendix A and Appendix B in the initial integrated review.

8. Dating period and storage conditions:

The dating period for reslizumab drug substance is 36 months at 2-8 ºC based on real time stability data from three process validation batches. The dating period is further supported by accelerated and stress stability data and supporting real time stability data from reslizumab DS lots manufactured by the commercial process For additional information see Appendix A in the initial integrated review.

C. Drug Product: Cinqair Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information on the characterization of Cinqair see Appendix A and Appendix B in the initial integrated review.

Table 3: Cinqair CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Origin	Risk	Control Strategy	Other
Protein content	General CQA Protein concentration (b) (4)	Safety and Efficacy	Reslizumab content is controlled during (b) (4) testing and as part of the DP release and stability specifications.	
Sterility and container closure integrity	Contamination. Sterility could be compromised by contaminants introduced throughout drug product manufacturing or through a Container closure integrity failure. Container closure integrity is a sterility assurance CQA.	Safety	Sterility is monitored as part of DP lot release and container closure is part of stability testing.	
Endotoxin	Contaminant that could be introduced throughout drug product manufacturing (b) (4)	Safety	Controlled (b) (4) as part of DP release specifications (b) (4)	
Sub-visible particulate (SVP)	SVP could form throughout manufacturing and during DP storage.	Safety (capillary occlusion) and Immunogenicity	Sub-visible particles (b) (4) are monitored at DP release.	The applicant addressed the Agency request (b) (4)
Visual Appearance	General CQA Appearance might be impacted by the formulation, but may also be an indicator of product	Safety and efficacy	Appearance is tested (b) (4) and included in DP release and stability specifications. Acceptance criteria are established for clarity, color, and visible	The applicant addressed the Agency request and revised the specifications for appearance to provide a better description of visible proteinaceous

	degradation or other changes to the product.		particulate matter. 100% manual inspection is performed for each DP batch. Reslizumab contains visible proteinaceous particulates. The product is administered by IV infusion. The infusion set includes an in-line filter.	particles and to indicate the DP must be free from foreign visible particles.
Extractable Volume	General CQA, (b) (4)	Safety and efficacy (low extractable volume)	Fill volume is part of the DP release specifications. Fill weight is controlled (b) (4)	The release acceptance criteria for extractable volume should be revised to reduce the overfill. This is a PMC.
pH	General CQA (b) (4) pH may be impacted on stability by breaches in container closure integrity or container closure leachables or changes in the product.	Safety and efficacy	pH is included during (b) (4) testing as well as part of DP release and stability specifications.	
Osmolality	General CQA (b) (4)	Safety	Osmolality is tested during (b) (4) DP processing and at release and stability.	
Leachables	Leachables could potentially be introduced by any product contact equipment, container closure and consumables.	Safety	Supported by leachables and extractables risk assessments for the product contact materials used in DP manufacture and storage and by stability studies.	

Cinqair Drug Product Quality Summary (Cont.)

1. Potency and Strength:

Potency is defined as the percent activity relative to reslizumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Cinqair will be available in an 10 mg/ml strength.

2. Summary of Product Design

Cinqair is presented in a single-dose glass vial containing 10 mg/ml of reslizumab. More than one vial may be needed to achieve the recommended dose of 3 mg/kg for a given patient depending of body weight. Cinqair is administered by intravenous infusion after dilution with saline USP. The infusion setting includes an in-line filter. For additional information see Appendix A in the initial integrated review.

3. List of Excipients

Each mL contains glacial acetic acid (0.12 mg), sodium acetate trihydrate (2.45 mg), and sucrose (70mg). For additional information see Appendix A in the initial integrated review.

4. Reference material(s),

The same reference materials are used for DS and DP. Refer to DS section. For additional information see Appendix A in the initial integrated review.

5. Manufacturing process summary

The drug product manufacturing process consists of (b) (4) 100% visual inspection, and packaging of vials.

Critical parameters selected for routine monitoring relate to (b) (4) The control strategy includes (b) (4) testing and release testing of final DP. Appropriate (b) (4) controls for microbial limits and sterility assurance are incorporated into the manufacturing process. For additional information see Appendix A and Appendix B in the initial integrated review.

6. Container closure

Cinqair is supplied as 10 ml vial containing 10 ml of reslizumab at the concentration of 10 mg/ml (100 mg). The container closure system consist of a 10 ml Type I clear borosilicate glass tubing vial, capped with a 20 mm stopper with (b) (4) a 20 mm aluminum crimp seal with royal blue flip-off cap. For additional information see Appendix A and Appendix B in the initial integrated review.

7. Dating period and storage conditions:

The dating period for drug substance is 36 months at 5 ± 3ºC.

8. List of co-packaged components: not applicable.

D. Novel Approaches/Precedents: N/A

E. Any Special Product Quality Labeling Recommendations

- Protect from light
- Do not freeze
- Do not shake

F. Establishment Information

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
DS production (b) (4) DS release and stability testing, DS storage, and MCB and WCB cell bank storage	(b) (4)	FEI: (b) (4)	7 item 483. Satisfactory response to 483 observations. Final inspection classification VAI	Approve
MCB and WCB cell bank production and storage		FEI: (b) (4)	N/A	Not applicable
Drug substance and finished drug product release and stability testing		FEI: (b) (4)	No 483 after PAI and GPM inspection.	Approve
Release and stability testing: (b) (4)	Teva Pharmaceutical Works Private Limited Company Site 1, Pallagi St. 13 Debrecen, 4042, Hungary	FEI: 3002806524	N/A	Approved based on profile
Drug substance release testing: (b) (4)	(b) (4)	FEI: (b) (4)	N/A	Facility approved based on profile

(b) (4)	(b) (4)			
Drug substance release testing: (b) (4)		FEI: (b) (4)	N/A	Facility approved based on profile
(b) (4)		FEI: (b) (4)	N/A	Facility approved based on profile
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
(b) (4) Labeling and Secondary Packaging of finished product Release& stability testing of finished product	(b) (4)	(b) (4)	N/A	Facility approved based on district recommendation

responsibilities				
Release & stability testing of finished product	(b) (4)	(b) (4)	See DS section	Approve
Release & stability testing of finished product		(b) (4)	See DS section	Approve
Release & stability testing of finished product: (Potency Bioassay)	Teva Pharmaceutical Works, plc. Pallagi Street 13 H-4042 Debrecen Hungary	3002806524	See DS section	Approve

G. Facilities

The subject BLA proposes manufacture and testing of reslizumab drug substance and drug product at the following facilities.

(b) (4) (FEI (b) (4)) is responsible for drug substance manufacture and (b) (4) release and stability testing of the DS (b) (4) also responsible for release and stability testing of the DP. A seven-item Form FDA 483 was issued to the firm at the end of the inspection (b) (4) The firm adequately addressed observations raised by the FDA 483. The final classification was VAI.

Cell banking operations will occur (b) (4)

(b) (4) is responsible for DP manufacture and release and stability testing of DP. This facility was approved based on district recommendation.

Additional testing operations for the DS and DP will occur at (b) (4) Teva Pharmaceutical Works Private Limited, Debrecen, Hungary (FEI 3006067169) (b) (4) A PAI inspection (b) (4) was conducted (b) (4) No FDA 483 was issued. This facility was approved based on district recommendation. The rest of the facilities were approved based on profile.

For additional establishment information see Appendix C in the initial integrated review.

H. Lifecycle Knowledge Management

a. Drug Substance

a. Protocols approved:
   i. Annual stability protocol, stability protocol (b) (4)
   ii. Qualification of new working reference standard
   iii. Qualification of new working cell banks
   iv. Chromatography (b) (4)

v. [redacted] protocols [redacted]

b. Outstanding review issues/residual risk: none (see Appendix A of this memo)
c. Future inspection points to consider: none

b. Drug Product

c. Protocols approved:
i. Annual stability protocol, stability protocol [redacted]

ii. Outstanding review issues/residual risk: none (see Appendix B of this memo)

d. Future inspection points to consider: none

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_____		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 team)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____			X	
Quality Considerations					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			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	

20 Pages have been Withheld in Full as duplicate copy of 2.5.16 and 2.1.16 reviews (e-p 55-73) below

BLA STN 761033

Reslizumab

Teva Pharmaceuticals

Ramesh Potla, PhD
Maria Teresa Gutierrez, PhD
Division of Biotechnology Review and Research III

OBP CMC Review Data Sheet

1. **BLA#:** STN 761033

2. **REVIEW DATE:** December 16, 2015

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Kathleen Donohue
Pharm/Tox: Carol Galvis
Product Quality Team: Ramesh Potla (drug substance), Tracy Denison (drug product)
OBP Immunogenicity: Joao Pedras-Vasconcelos
Product Quality Microbiology (DS): Bo Chi
Product Quality Microbiology (DP): Laskhmi Narasimhan
BMT or Facilities: Thuy Nguyen
Clinical Pharmacology: Yunzao Ren
Statistics: Lan Zeng
OBP Labeling: Jibril Abdus-Samad
OBP RPM: Andrew Shiber
Clinical RPM: Colette Jackson

4. **MAJOR GRMP DEADLINES**
Filing Meeting: May 11, 2015
Mid-Cycle Meeting: August 28, 2015
Wrap-Up Meeting: February 04, 2016
Primary Review Due: December 16, 2015
Secondary Review Due: December 23, 2015
PDUFA Action Date: March 30, 2016

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

Communication/Document	Date
Information Request 1	May 11, 2015
Information Request 2	July 13, 2015
Information Request 3	August 24, 2015
Information Request 4	September 24, 2015
Information Request 5	October 5, 2015
Information Request 6	October 19, 2015
Information Request 7	October 29, 2015
Information Request 8	November 16, 2015
Information Request 9	November 18, 2015
Information Request 10	November 25, 2015
Information Request 11	December 1, 2015
Information Request 12	December 2, 2015
Information Request 13	December 3, 2015
Information Request 14	December 11, 2015

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

Submission	Date Received	Review Completed* (Yes/No)
Original submission	March 30, 2015	Yes
Amendment 3	May 22, 2015	Yes
Amendment 9	August 7, 2015	Yes
Amendment 14	September 11, 2015	Yes
Amendment 17	September 30, 2015	Yes
Amendment 20	October 9, 2015	Yes
Amendment 24	October 30, 2015	Yes
Amendment 25	November 5, 2015	Yes
Amendment 26	November 9, 2015	Yes
Amendment 28	November 23, 2015	Yes
Amendment 29	November 24, 2015	Yes
Amendment 30	November 30, 2015	Yes
Amendment 32	December 2, 2015	Yes
Amendment 34	December 4, 2015	Yes
Amendment 35	December 7, 2015	Yes
Amendment 36	December 7, 2015	Yes
Amendment 37	December 7, 2015	Yes

*All or portions of the content of the communications would be directed to the appropriate CMC reviewer (drug product, drug substance, immunogenicity, micro)

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Cinqair
   b. Trade Name: Cinqair
   c. Non-Proprietary/USAN: reslizumab
   d. CAS name: 241473-69-8
   e. Common name: CEP-38072
   f. INN Name: Reslizumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMANIZED (IGG4) [redacted] (b) (4) (IL5_HUMAN) [CEP38072]
   i. Other Names: CEP-38072, CTx55700, SCH 55700

8. **PHARMACOLOGICAL CATEGORY:** anti-interleukin 5 monoclonal antibody
9. **DOSAGE FORM:** Injection
10. **STRENGTH/POTENCY:** 10 mg/mL
11. **ROUTE OF ADMINISTRATION:** intravenous infusion
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted] (b) (4)			Yes	I reviewed the Master File and found it acceptable to support BLA 761033

*This Biologics Master File relates to drug substance only

13. **INSPECTIONAL ACTIVITIES**

This pre-license inspection of the drug substance manufacturing facility [redacted] (b) (4) was conducted [redacted] (b) (4) following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, under FACTS assignment # [redacted] (b) (4) The inspection covered drug substance manufacturing areas [redacted] (b) (4) and warehouse [redacted] (b) (4) and an offsite warehouse [redacted] (b) (4) The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products; CP 7346.832, Pre-Approval Inspections/Investigations; and ICH Q7. This inspection was limited to the manufacturing of reslizumab [redacted] (b) (4)

A seven-item 483 was issued. See Appendix 1 for a copy of FDA-483. The recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived.

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
Maria-Teresa Gutierrez-Lugo, Ph.D. Application Technical Lead Division of Biotechnology Research and Review III Office of Biotechnology Products	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=001181 8863, cn=Maria Teresa Gutierrez Lugo -S Date: 2015.12.16 22:03:44 -05'00'
Ramesh Potla, Ph.D. Primary Reviewer Division of Biotechnology Research and Review III Office of Biotechnology Products	Ramesh B. Potla -S Digitally signed by Ramesh B. Potla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012 101865, cn=Ramesh B. Potla -S Date: 2015.12.16 21:45:45 -05'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of STN 761033 for Cinqair (reslizumab). The data submitted in the Biologics License Application support the conclusion that the manufacture of Cinqair (reslizumab) is well controlled and leads to a product that is pure and potent. The reslizumab drug substance is free from endogenous and adventitious agents sufficient to meet the parameters recommended by the FDA. The conditions used for manufacturing reslizumab drug substance have been sufficiently validated, and consistent product has been manufactured from the multiple production runs. The Office of Biotechnology Products recommends Cinqair (reslizumab) be approved for human use (under conditions specified in the package insert).

The Office of Biotechnology Products recommends an expiry period of 36 months for reslizumab drug substance when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirement

If the BLA is approved, two Post-Marketing Commitments (PMCs) should be agreed upon. The following is draft PMC language:

1. To improve the overall control strategy of the drug substance manufacturing process (b) (4)
2. To implement a (b) (4) in the drug substance manufacturing process.

The final study report(s) for the two PMCs will be reported according to 21 CFR 601.12

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

Refer to Review by Dr. Jibril Abdus-Samad

VI. Review Of Common Technical Document-Quality Module 3.2

Find below review of 3.2.S. Refer to Dr. Tracy Denison's review for Section 3.2.P.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Refer to review by Dr. Joao Pedras-Vasconcelos

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

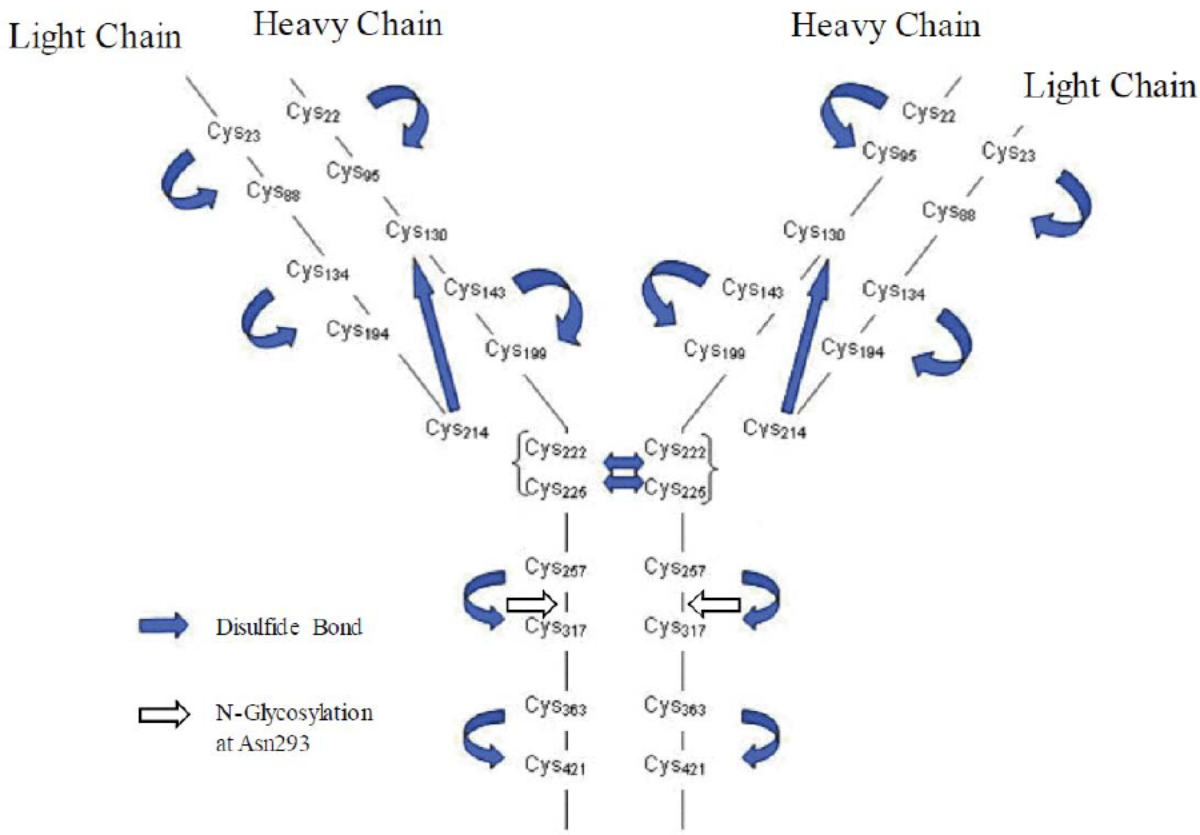
Unless explicitly indicated, all figures and tables in this review are copied directly from the BLA submission or from information request responses.

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

Reslizumab (CEP-38072) is a recombinant, humanized IgG_4, κ monoclonal antibody to the human interleukin-5 (anti-IL-5 MAb). Reslizumab contains the complementary determining regions (CDRs) of the original rat antihuman antibody 39D10 grafted onto a human framework. It is composed of two light chains and two heavy chains linked by 12 intra-chain and 4 inter-chain disulfide bonds. (b) (4) N-linked (b) (4) oligosaccharides of reslizumab are derived from NS0 cell lines. The predicted molecular mass is 146.8 kDa. The schematic diagram of reslizumab is shown below:

Figure 1: Structural Representation of Reslizumab Disulfide Bond Linkage



The predicted amino acid sequence of reslizumab is provided below:

Table 1: Theoretical Amino Acid Sequence for Reslizumab

(b) (4)

Light Chain

(b) (4)

Reviewer Comment: (b) (4)

3.2.S.1.3 General Properties

Reslizumab is a humanized IgG_4, κ monoclonal antibody produced in a NS0 cell line. Reslizumab binds to soluble circulating human IL-5 and prevents its binding to the IL-5 receptor on eosinophils, thereby inhibiting their proliferation and activation. The drug substance (DS) contains reslizumab at (b) (4) mg/mL concentration (b) (4) The properties of reslizumab are provided in the table below:

Table 1: Reslizumab Drug Substance General Properties

Property	Description
Appearance Clarity and degree of opalescence of a liquid	Clear to slightly hazy/opalescent solution
Appearance Degree of coloration	Colorless to slightly yellow/yellow solution
Protein type	Human IgG4, kappa
Amino acid sequence	Section 3.2.S.1.2, Table 1
Molecular mass (theoretical)	146,776 Da (b) (4)
Glycosylation	N-Glycosylated at Asn293 (b) (4)
UV Extinction coefficient at the wavelength of A (b) (4)	(b) (4)
pH at (b) (4) °C	
Protein concentration	
pI of main peak	
Osmolality	
Thermodynamics	
Sedimentation coefficient	
Disulfide linkage	16 disulfide bonds
Biological activity	Inhibition of proliferation of (b) (4) cells Potency (b) (4) % relative potency

Reviewer Comment: (b) (4) *The recommended storage conditions for both DS and DP are 5±3 °C.*

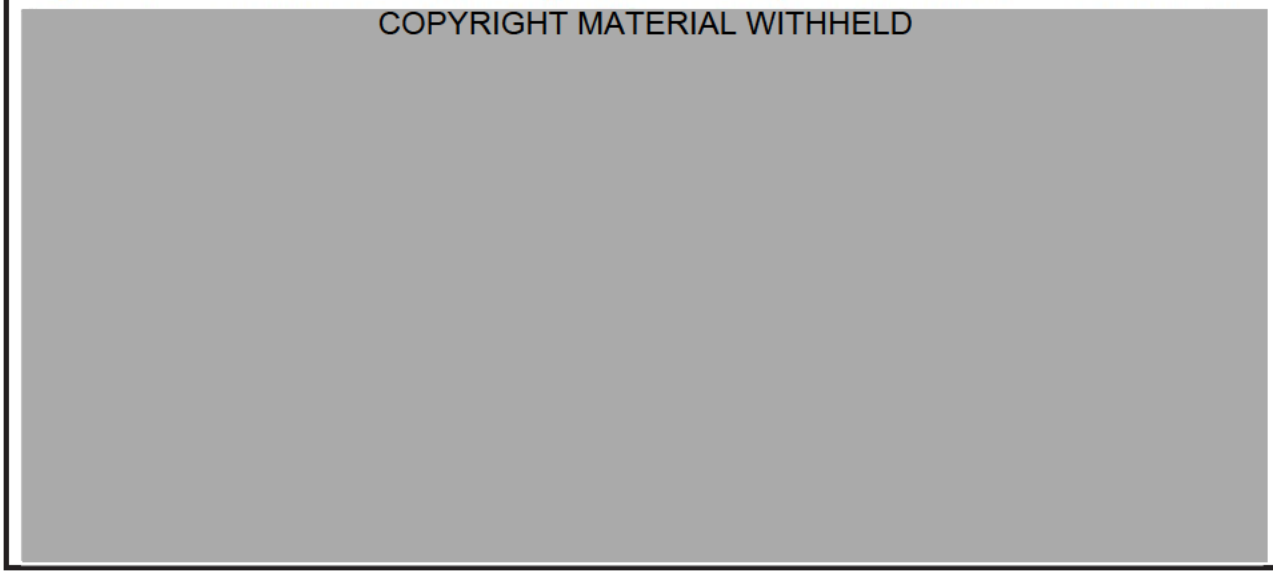
Reslizumab's Mechanism of Action:

Reslizumab is a humanized IgG4 monoclonal antibody that binds to and neutralizes human IL-5. IL-5 mediates the proliferation, activation, and survival of target eosinophil cells. The mechanism of action for reslizumab is achieved by blocking IL-5 binding capacity to its specific receptor. Using a combination of synthetic peptide mapping and site-directed mutagenesis studies, it is determined that reslizumab recognizes a tetrapeptide with amino acid residues 89 – 92 (E89, R90, R91, and R92) as the minimal epitope on human IL-5. In addition, results from amino acid substitution studies showed that an additional three amino acid residues (K85, G87, and N94)

located in the vicinity of the minimal epitope region also impact the binding of reslizumab to IL-5 (Zhang et al, 1999). Three (E89, R90, and R91) out of 4 amino acid residues located in the minimal epitope region of human IL-5 are also confirmed as key residues for the interaction of IL-5 with human IL-5 receptor α complex (Graber, 1995; Tavernier, 1995; and Patino et al, 2011). Overall, the provided information demonstrate that reslizumab neutralizes soluble IL-5 and prevents this cytokine from binding to IL-5 receptor α, thereby preventing the activation of eosinophils and their consequent mobilization into the bronchial airspace. See Figures 1 and 2 below for schematic diagram(s) on reslizumab's mechanism of action.

Figure 1: Reslizumab Mechanism of Action

Figure 2: Human IL-5 Interacting with IL-5 Receptor α at Residues E^{89}, R^{90}, and R^{91}



3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Reslizumab DS is manufactured [redacted] (b) (4) for Teva Pharmaceuticals. The manufacturing, testing and storage sites for reslizumab DS are shown in the table below:

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

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

Office of Biotechnology Products
Division of Biotechnology Research and Review III
Silver Spring, MD 20993

Memorandum of Review

STN:	BLA761033
Subject:	Drug Substance Product Quality Amendment to OPQ Original BLA761033
Date:	02/05/2016
Review/Revision Date:	12/20/2015
Primary Reviewer:	Ramesh Potla, Ph.D. Ramesh B. Potla -S Digitally signed by Ramesh B Potla -S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 0012101865 cn Ramesh B Potla -S Date: 2016 02 11 16:51:39 05'00'
Secondary Reviewer:	Maria Gutierrez-Lugo, Ph.D. Maria Teresa Gutierrez Lugo -S Dig tally signed by Maria Teresa Gutierrez Lugo -S DN c=US o=U S Gove nment ou=HHS ou=FDA ou=People 0 9 2342.19200300 100 1 1=0011818863 cn=Maria Teresa Gutierrez Lugo -S Date: 2016 02 11 17 36 00 05 00'

BACKGROUND

As per CDER 21st Century Review Guidelines, the product quality review for BLA761033 was completed and submitted into Panorama on December 16, 2015. However, at that time 9 outstanding issues were yet to be resolved because information requests were submitted to the Sponsor late in the review cycle. This amendment provides an evaluation of all outstanding review issues.

The review is organized as follows:

1. In Bold font is the FDA information request.
2. In normal font is a summary of the Sponsor's response.
3. In italic font is the reviewer's evaluation of the Sponsor's response.

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

IR December 11, 2015

1. **Your proposed release specifications for drug substance (DS) and drug product (DP) are not supported by your clinical and manufacturing experience. In addition, we note that there were several safety signals observed in the reslizumab clinical studies. The mechanisms underlying**

these safety signals and their potential relationship with product quality attributes remain unclear. For this reason, revise the acceptance criteria for the following test methods to align with your clinical experience from pivotal studies:

(a) For potency, the proposed acceptance criteria for DS and DP are (b) (4) % of the reference standard. These criteria are (b) (4) your clinical experience. The potency of clinical lots, and from lots manufactured using the (b) (4) commercial process and measured by (b) (4) assay, ranged between (b) (4) % for DS and (b) (4) % for DP.

Sponsor's Response: Teva revised the potency acceptance criteria to (b) (4) % based on a calculated 95% confidence, 99% coverage two-sided tolerance interval of (b) (4) % from DS and DP release and stability data from the (b) (4) assay.

Reviewer Comment: *The Sponsor response is acceptable the proposed acceptance criteria of (b) (4) % provide a better control of the potency attribute, when compared to the originally proposed acceptance criterion of (b) (4) %. The proposed specifications are based on release and stability data from a limited number of DS and DP batches. The Sponsor is committed to revise the potency specification upon gathering additional data once sufficient number of reslizumab DS and DP batches are manufactured (n=30).*

(b) For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4) % (b) (4) For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4) % (b) (4) and ≤ (b) (4) % (b) (4) These criteria are not reflective of clinical and at-scale manufacturing experience. We note that the following ranges were observed for DS and DP– (b) (4) all pivotal clinical lots were above (b) (4) % (b) (4) ; (b) (4) the pivotal clinical lots were above (b) (4) % (b) (4) and (b) (4) % (b) (4)

Sponsor's Response: Teva provided the following information:

(i) Based on the assay variability ((b) (4) %) and the criticality of the attribute, Teva proposes to retain the orig nal acceptance criteria of ≤ (b) (4) % (b) (4)

(ii) (b) (4) Teva used a two-sided confidence interval analysis and revised the (b) (4) acceptance criteria to ≤ (b) (4) % and ≥ (b) (4) %, respectively.

Reviewer Comment: *The Sponsor response is acceptable because the proposed specifications are based on release and stability data from a limited number of DS and DP batches. The Sponsor is committed to revise the* (b) (4) *specification upon gathering additional data once sufficient number of reslizumab DS and DP batches are manufactured (n=30).*

(c) For (b) (4) **the proposed acceptance criteria for DS and DP are:** (b) (4) **%. We note that the following ranges were observed from your clinical and manufacturing experience –** (b) (4) **% for DS and** (b) (4) **for DP,** (b) (4) **:** (b) (4) **% for DS and** (b) (4) **for DP, and** (b) (4) **:** (b) (4) **% for DS and** (b) (4) **for DP.**

Sponsor's Response: (b) (4)

Reviewer Comment: *The Sponsor response was not acceptable.* (b) (4) *Therefore, the following additional information request was sent to Teva on December 23, 2015.*

"The release and stability (b) (4) specifications for reslizumab drug substance and drug product provides quantitative acceptance criteria for monitoring and controlling the following (b) (4)

Revise your (b) (4) specification (b) (4)

Provide the revised (b) (4) specifications along with a justification to support the proposed additional acceptance criteria."

Teva provided an IR response on January 05, 2016. In their IR response, Teva appropriately established the following additional acceptance criteria for (b) (4) *release and stability specification:*

(b) (4)

(b) (4)

I consider the Sponsor's response acceptable (b) (4) *and that the Sponsor is committed to revise the* (b) (4) *specifications upon gathering additional data once sufficient number of reslizumab DS and DP batches are manufactured (n=30).*

(d) For (b) (4) **the proposed acceptance criteria for DS and DP are ≥** (b) (4) **% and ≤** (b) (4) **% The observed levels were consistently in the range of** (b) (4) **% for both DS and DP.**

Sponsor's Response: Teva tightened the acceptance criteria (b) (4) to ≤ (b) (4) % and t (b) (4) to ≥ (b) (4) %.

Reviewer Comment: *The Sponsor response is acceptable because the proposed specifications are based on release and stability data from a limited number of DS and DP batches. The Sponsor is committed to revise the* (b) (4) *specification upon gathering additional data once sufficient number of reslizumab DS and DP batches are manufactured (n=30).*

(e) For (b) (4) **impurity, the proposed acceptance criteria for DS are ≥** (b) (4) **ng/mg** (b) (4) **The levels** (b) (4) **in your commercial and pivotal clinical material ranged between** (b) (4) **ng/mg** (b) (4)

Sponsor's Response: Teva tightened the (b) (4) acceptance criterion to ≤ (b) (4) ng/mg (b) (4) based on potential lot-to-lot variability associated with (b) (4) the limited lots (b) (4) used in the manufacturing process.

Reviewer Comment: *The Sponsor response is acceptable because the proposed specifications are based on release data from a limited number of DS batches. The Sponsor is committed to revise the* (b) (4) *specification upon gathering additional data once sufficient number of reslizumab DS batches are manufactured (n=30).*

2. In your BLA, you propose to include (b) (4) **testing sites for** (b) (4) **testing of reslizumab DS by the** (b) (4) **method. You provided a study report (ESPI-11776) in support of the transfer of the** (b) (4) **assay** (b) (4) **Your assay transfer evaluation was conducted with** (b) (4) **samples** (b) (4) **In addition to the difference** (b) (4)

were different. Therefore, since the assay was not properly transferred, you should remove testing by method from the testing responsibilities

Sponsor's Response: Teva removed as a testing site by method. The test by will continue to be conducted at facility.

Reviewer Comment: *The Sponsor response is acceptable.*

3. **In a response to Information Request dated 04th December 2015, you provided information This is not acceptable. Set that is supported by process validation studies and available data from at-scale batches demonstrating clearance of this impurity.**

Sponsor's Response: Teva established the total amount that can be used in the reslizumab drug substance manufacturing process.

Reviewer Comment: *Responding to a previous Information Request dated November 16, 2015; Teva provided a table with the total amounts for all drug substance batches manufactured to date. Teva used during manufacture of reslizumab DS batch 89182. DS batch 89182 is one of the original process performance qualification batches manufactured at the commercial scale and was used in the pivotal clinical studies. Process validation data provided in the BLA submission for DS batch 89182 demonstrated adequate clearance Therefore, the proposed is acceptable.*

4. **We note that the container used for reslizumab DS is composed of**

Provide a risk assessment on the use of container system for reslizumab DS with regards to the potential impact from leachable.

Sponsor's Response: Teva provided an extractable study report of container system – for reslizumab (Report# -001-10R). The study results show that was not identified as a potential leachable in the extractable study. However, one of the species detected in the extractable study, namely , is closely related To further assess the risk as a potential leachable, Teva performed a leachable study using container for bulk drug substance at 2-8°C for 36 months (Report TR-Q-22) was not detected in the leachable study at the sensitivity levels of µg/mL.

Reviewer Comment: *The Sponsor response is acceptable because they provided sufficient information showing no safety risk to patients. The cytotoxic leachables were not identified in the real-time leachable studies under the actual conditions of use (final container closure contained drug substance) throughout the proposed shelf-life of 36 months.*

5. **In Section 3.2.R. Regional Information of your BLA, you provided an incorrect SOP for assay. Update your BLA with the correct SOP for assay.**

   Sponsor's Response: Teva acknowledged the error and provided the correct SOP for the Assay (Method-TS003800-R04-).

   Reviewer Comment: *The Sponsor response is acceptable.*

6. **The post-approval stability protocol and stability commitment sections (3.2.S.7.2 and 3.2.P.8.2) do not specify whether you intent to submit data from the stability studies to the Agency. Revise sections 3.2.S.7.2 and 3.2.P.8.2 to specify commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.**

   Sponsor's Response: Teva revised the post-approval stability protocol and stability commitment sections of the BLA to specify commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports. Teva also clarified that they request approval of post-

approval stability protocols (b) (4)

Reviewer Comment: *The Sponsor response is acceptable.*

7. **In a response to Information Request dated 07th December 2015, you provided information on the stability assessment of the working reference standard. Your proposed stability acceptance criteria are inadequate** (b) (4) (b) (4) **Revise your working reference standard protocol** (b) (4)

Sponsor's Response: Teva revised the working reference standard (WRS) stability protocol to include the following information:

(i) Attributes that are used to confirm the suitability of the WRS as a control measure for assay system suitability include (b) (4) These attributes will be compared to the approved DS acceptance criteria.

(ii) To prevent a potential drift in WRS potency over time, the Sponsor will test the WRS against the primary RS (b) (4) The stability acceptance criterion requires (b) (4) % of the original WRS potency release value.

Reviewer Comment: *The Sponsor response is acceptable because the proposed relative potency stability acceptance criteria of ± (b) (4)% is within the demonstrated assay variability (intermediate precision value of (b) (4)% from potency method validation report) for potency. The stability acceptance criteria of ± (b) (4)% would therefore provide a meaningful control in preventing drift in potency result of WRS throughout the duration of its intended use.*

8. **You provided data on the characterization of the levels of (b) (4) for batch 202709ARS in your BLA submission. Provide data on the levels (b) (4) in reslizumab throughout development,**

including batches used in clinical studies that you intend to use to support your application. In addition, describe your control strategy for relative levels [redacted] in your product.

Sponsor's Response: Teva provided characterization data on the levels [redacted] for several reslizumab DS batches, including the DS batches used to produce the pivotal clinical material (89170, 89182, 89991, and 202709). The data were obtained using a [redacted] method, which determines the content [redacted] released from [redacted] reslizumab samples. See Table 1 below for the levels [redacted] in reslizumab DS batches:

Table 1: [redacted] Content in Reslizumab Batches throughout Development, including Batches used in the Clinic

[redacted]

Reviewer Comment: *Provided data show that the levels [redacted] were pretty much consistent throughout reslizumab development at approximately [redacted]% and [redacted]%, respectively. Therefore, I agree with the Sponsor's claim that the levels [redacted] is well controlled during the manufacturing process.*

9. **In response to your Information Request dated 07th December 2015, you propose to update the [redacted] to include current release DS acceptance criteria. This approach would be acceptable provided the DS release acceptance criteria are revised as described in comment 1 above. However, your proposal [redacted] is not acceptable. [redacted]**

(b) (4)

Sponsor's Response: Teva provided the updated (b) (4) protocols on January 15, 2016. In the revised protocols, Teva provided the following information:

(i) (b) (4)

(ii) The protocol retained the original DS release acceptance criteria. See Tables below for the proposed acceptance and additional acceptance criteria (b) (4)

(b) (4)

(b) (4)

(iii)

(b) (4)

[redacted]

(iv) [redacted]

Reviewer Comment: *The Sponsor response is acceptable, with one exception. In their IR response dated December 15, 2015; Teva committed to revise the protocol to include the updated DS release acceptance criteria as described in Question 1 response. However, the protocols provided to the Agency on January 15, 2016 still include the originally proposed acceptance criteria. This discrepancy might have occurred because Teva did not receive Agency's concurrence on the newly proposed DS release acceptance criteria by the time they formalized the* [redacted] *protocols. This is not an approvability issue because the* [redacted] *lots must eventually meet the current specifications for drug substance release. During the next inspection, the investigator should follow up to see if the Sponsor revised the protocol through an appropriate change control system to include the agreed upon DS release specifications as the protocol acceptance criteria.*

Current Status of Post-Marketing Comment #3: [redacted]. During inspection of the [redacted] facility, we noticed [redacted] This was one of the 483 observations. The Sponsor was also asked to agree to the following post-marketing commitment (PMC 3):

"To implement a [redacted] in the drug substance manufacturing process." The final study report will be submitted according to 21 CFR 601.12.

Responding to the 483, [redacted] provided information [redacted] Teva is currently seeking Agency's feedback on whether information provided in this study report is sufficient [redacted]

Reviewer Comment: *The study report identified* [redacted]

(b) (4)

(b) (4)

it is not possible to perform a risk assessment of the impact on patients receiving reslizumab.

On February 5, 2016, an IR requesting additional information on the potential leachables (b) (4) *was sent to Teva. Teva provided the requested information on February 10, 2016 . However, as part the IR, Teva stated that they have reconsidered PMC#3. Teva commits to implementing this change prior to the next reslizumab manufacturing campaign.*

OVERALL REVIEWER CONCLUSION:

The Sponsor's responses to the information requests of December 11, 2015 and subsequent follow-ups are acceptable. There is no impact on our recommendation for BLA approval.

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

Office of Biotechnology Products
Division of Biotechnology Research and Review III

Memorandum of Review

STN: BLA 761033

Subject: Drug Product Quality Review Addendum to OPQ Original BLA 761033

Date: February 1, 2016

Primary Reviewer: Tracy Denison, PhD

Tracy A. Denison -S
Digitally signed by Tracy A Denison S
DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0 9 2342 19200300 100 1 1=2001154781, cn=Tracy A Denison S
Date: 2016 02 08 17:25:50 05'00'

Secondary Reviewer: Maria Teresa Gutierrez, PhD

Maria Teresa Gutierrez Lugo -S
Dig tal y s gned by Maria Teresa Gutierrez Lugo S
DN c=US o=U S Government ou=HHS ou=FDA ou=Peop e 0 9 2342 19200300 100 1 1=00118 18863 cn=Maria Teresa Gutierrez Lugo S
Date 2016 02 11 17 34 02 05'00'

BACKGROUND

As per CDER 21st Century Review Guidelines, the product quality reviews for BLA 761033 were completed and submitted into Panorama by December 16, 2015. However, at that time there were some outstanding issues that were yet to be resolved because some information requests were still pending a response from the sponsor. This addendum provides an evaluation of all outstanding review issues that pertain to the drug product quality review.

This addendum is divided into sections based on the response to different information requests received from the sponsor after the reviews were submitted into Panorama. Each section is generally formatted as follows:

a) In **bold font** is the FDA information request.
b) In normal font is a summary of the sponsor's response.
c) In *italic font* is the reviewer's evaluation of the sponsor's response.

In summary, all product quality issues for the drug product section of BLA 761033 are resolved. For some information requests, the response was relevant to both drug substance and drug product review. The reader is also referred to the addendum of the drug substance review by Dr. Ramesh Potla for additional review commentary. This may be particularly relevant for review of changes to specifications that apply to both drug substance and drug product.

I. FDA Information Request - December 11, 2015, FDA

(Only questions relevant to drug product are shown.)

FDA'S QUESTION 1:
Your proposed release specifications for drug substance (DS) and drug product (DP) are not supported by your clinical and manufacturing experience. In addition, we note that several safety signals were observed in the reslizumab clinical studies. The mechanisms underlying these safety signals and their potential relationship with product quality attributes remain unclear. Therefore, you should revise the DS and DP acceptance criteria for the following test methods to align with your clinical experience from pivotal studies:

(a) For potency, the proposed acceptance criteria for DS and DP are (b) (4) % of the reference standard. These criteria are (b) (4) your clinical experience. The potency of clinical lots, and from lots manufactured using the (b) (4) commercial process and measured by the current (b) (4) assay, ranged between (b) (4) % for DS and (b) (4) % for DP.

(b) For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4) % (b) (4) For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4) % (b) (4) and ≤ (b) (4) % (b) (4) These criteria are not reflective of clinical and at-scale manufacturing experience. We note that the following ranges were observed for DS and DP– (b) (4) all pivotal clinical lots were above (b) (4) % (b) (4) ; (b) (4) all the pivotal clinical lots were above (b) (4) % (b) (4) and (b) (4) % (b) (4)

(c) For (b) (4) the proposed acceptance criteria for DS and DP are: (b) (4) . We note that the following ranges were observed from your clinical and manufacturing experience – (b) (4) % for DS and (b) (4) for DP, (b) (4) : (b) (4) % for DS and (b) (4) for DP, and (b) (4) : (b) (4) % for DS and (b) (4) for DP.

(d) For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4) % (b) (4) and ≤ (b) (4) % (b) (4) The observed (b) (4) levels were consistently in the range of (b) (4) % for both DS and DP.

(e) For the (b) (4) impurity, the proposed acceptance criteria for DS are ≥ (b) (4) ng/mg (b) (4) The levels (b) (4) in your commercial and pivotal clinical material ranged between (b) (4) ng/mg (b) (4)

(f) In response to an information request dated Dec2, 2015, you propose to update the acceptance criteria for the DP specification - Appearance, Visible Particle Matter from [redacted] to "May contain translucent to white, amorphous proteinaceous particles". In addition to implementing this proposed update, revise your acceptance criteria to also specify that the product should be free from foreign material.

FDA'S QUESTION 6:
The post-approval stability protocol and stability commitment sections (3.2.S.7.2 and 3.2.P.8.2) do not specify whether you intent to submit data from the stability studies to the Agency. Revise sections 3.2.S.7.2 and 3.2.P.8.2 to specify commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.

Sponsor's Response:
The sponsor's responses to these questions are summarized below. Most of these responses, except where noted, were submitted by the sponsor to the Agency on December 15, 2015.

Question 1a – On December 22, 2015 the sponsor responded to this request and adjusted the potency criteria to [redacted]%.

Question 1b – The sponsor proposed [redacted] The sponsor agreed to tighten the criteria [redacted] to ≤ [redacted]% and ≥ [redacted]%, respectively.

Question 1c – the sponsor proposed [redacted] However, following another information request by FDA the sponsor adjusted this specification further which is discussed in the last section of this memorandum.

Question 1d – The sponsor agreed to tighten the acceptance criteria for % [redacted] to be ≤ [redacted]% [redacted] and ≥ [redacted]% [redacted]

Question 1e – This subpart of this question is relevant only to a drug substance specification. See the addendum to the drug substance review for more information.

Question 1f – The sponsor agreed to the proposed changed and the specification for appearance of the drug product was changed to "May contain translucent to white, amorphous proteinaceous particles. Free from foreign material."

Question 6 – The sponsor revised the post-approval stability protocol and stability section 3.2.P.8.2 to specify commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.

Reviewer's Comment: The responses are acceptable. There was some disagreement regarding the need to change the (b) (4) *specification, however following another information request on December 24, 2015 the sponsor adjusted the criteria (see last section of this memorandum). The reader is also referred to the drug substance addendum review by Dr. Ramesh Potla for additional review discussion regarding the specifications that are commonly shared for the drug substance and drug product.*

A PMC was agreed upon with Teva to further revise the DS and DP release and stability specifications after additional manufacturing experience is acquired. Refer to approval letter for a list of all PMCs.

II. FDA Information Request - December 17, 2015

(Only questions relevant to drug product are shown.)

FDA'S QUESTION 2:

(b) (4) **Please clarify whether you are requesting approval of the post-approval stability protocols defined in sections 3.2.S.7.2 and 3.2.P.8.2.** (b) (4)

Sponsor Response: On December 22, 2015 the sponsor confirmed they propose (b) (4) and that they are requesting approval for the post-approval stability protocols (b) (4)

Reviewer's Comment: The response is acceptable.

FDA'S QUESTION 3:

We note that you recently amended your BLA submission (b) (4) **Revise your post-approval stability protocol for drug product** (b) (4)

Sponsor Response: On December 22, 2015 the sponsor agreed (b) (4)

Reviewer's Comment: The response is acceptable.

FDA'S QUESTION 4:
The preparation and administration instruction of your proposed labeling indicate that your product is "compatible with polyvinylchloride (PVC) or polyolefin infusions bags". The in-use compatibility data for the polyolefin infusion bags included two studies (study 1a and 2a of Table 1 of section 3.2.P.2.6). These studies did not include evaluation of potency, sub-visible particles, (b) (4) **In addition, the studies did not evaluate reslizumab infusion preparations relevant to low and high body weight of the treatment populations and did not evaluate the product at 2-8 °C. To support the compatibility of your product with the polyolefin infusion bag, provide potency, sub-visible particles,** (b) (4) **data. Data to support reslizumab infusion preparations relevant to low and high patient body weight, and storage temperatures described in your product labeling should also be provided. You may use a similar experimental design as the one conducted for study 3 of Table 1 of Section 3.2.P.2.6. Also submit in your report representative raw data from the** (b) (4) **results from the completed study 3 and the study conducted to support the use of polyolefin infusion bag. Alternatively, in lieu of providing these study results, you may remove the use of the polyolefin bag from the product labeling.**

Sponsor Response:
On January 13, 2016 the sponsor responded to part of this information request. Data for appearance, protein concentration, osmolality, (b) (4) and HIAC particle counts were provided in the response. The sponsor indicated the potency results were still being generated and would be submitted later. On January 29, 2016, the sponsor provided the following updated table showing all results of the compatibility testing of the product when used in the polyolefin infusion bag, including the pending potency results.

Table 1: Summary of Analytical Results for the In-use Polyolefin IV Bag

(b) (4)

[redacted]

Reviewer's Comment: The data support that the product is compatible with the polyolefin infusion bag as proposed on the draft label for the product. The product retains purity, potency, and other physicochemical attributes in the polyolefin bag infusion at both room and refrigeration temperatures for up to (b) (4) *hours. The data cover the conditions directed in the label and relevant preparations for the expected range of patient weights, so the claim that polyolefin infusion bags are suitable for use to administer the product is justified.*

III. FDA Information Request – December 24, 2015

(Only questions relevant to drug product are shown.)

FDA'S QUESTION 1:

The release and stability (b) (4) **specifications for reslizumab drug substance and drug product provides quantitative acceptance criteria for monitoring and controlling the following** (b) (4) [redacted] **Revise your** (b) (4) **specification** (b) (4) [redacted] **Provide the revised** (b) (4) **specifications along with a justification to support the proposed additional acceptance criteria.**

Sponsor Response:
On January 5, 2016 the sponsor responded to the information request. They agreed to implement limits (b) (4) as indicated in the following box.

(b) (4)

The sponsor is also committed to assessing the appropriateness of the limits after another 10 batches are manufactured.

Reviewer's Comment: The adjusted limits are acceptable. (b) (4)

First approval for indication

Recommendation: Approval

BLA 761033
Review 1
December 23, 2015

Drug Name/Dosage Form	Cinqair/injection
Strength/Potency	100 mg/10 ml (10 mg/ml)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Proposed Indication	To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.
Applicant/Sponsor	Teva Pharmaceuticals

a. Names

i.	Proprietary Name:	Cinqair
ii.	Trade Name:	Cinqair
iii.	Non-Proprietary/USAN:	reslizumab
iv.	CAS name:	241473-69-8
v.	Common name:	CEP-38072
vi.	INN Name:	reslizumab
vii.	OBP systematic name:	MAB HUMANIZED (IGG4) (b) (4) (IL5_HUMAN) CEP38072]
viii.	Other Names:	CEP-38072, CTx55700, SCH 55700

b. Pharmacology category: anti-interleukin 5 monoclonal antibody

Product Overview

Cinqair (reslizumab) is a humanized IgG4, kappa anti-IL5 monoclonal antibody produced in NS0 cells. Reslizumab contains the complementary determining regions (CDRs) of the original rat anti-human antibody 39D10 grafted onto a human framework. Reslizumab is glycosylated at the Fc region. The N-linked oligosaccharides of reslizumab are (b) (4) derived from NS0 cell lines. The predicted molecular mass is 146.8 kDa. Reslizumab binds to and neutralizes human IL-5. IL-5 mediates the proliferation, activation, and survival of target eosinophil cells. The mechanism of action for reslizumab is achieved by blocking IL-5 binding to its specific receptor.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/ DIVISION
Drug Substance	Ramesh Potla	Division of Biotechnology Review and Research III
Drug Product	Tracy Denison	Division of Biotechnology Review and Research III
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	Lakshmi Narasimhan	Division of Microbiology Assessment
Facilities	Thuy Nguyen	Division of Inspectional Assessment
Immunogenicity*	Joao Pedras-Vasconcelos	Division of Biotechnology Review and Research III
Immunogenicity*	Amy Rosenberg	Division of Biotechnology Review and Research III
Immunogenicity*	Susan Kirshner	Division of Biotechnology Review and Research III
Drug substance and Drug Product Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment
Business Regulatory Project Manager	Andrew Shiber	OPRO
Application Technical Lead	Maria-Teresa Gutierrez-Lugo	Division of Biotechnology Review and Research III
Tertiary Reviewer	Susan Kirshner	Division of Biotechnology Review and Research III

* The immunogenicity review is filed as a separate memo

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Colette Jackson	ODEII/DPARP
Cross-disciplinary Team lead	Banu Karimi-Shah	ODEII/DPARP
Clinical Reviewer	Kathleen Donohue	ODEII/DPARP
Pharm/Tox	Carol Galvis, Marcie Wood	ODEII/DPARP
Clinical Pharmacology	Yunzao Ren, Ping Ji	OCP
Statistics	Lan Zeng	OB/DBIV

Quality Review Team - Signature Page

DISCIPLINE	REVIEWER	BRANCH/ DIVISION	e-Signature
Drug Substance	Ramesh Potla	Division of Biotechnology Review and Research III	
Drug Product	Tracy Denison	Division of Biotechnology Review and Research III	
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment	
Microbiology Drug Product	Lakshmi Narasimhan	Division of Microbiology Assessment	
Facilities	Nguyen, Thuy	Division of Inspectional Assessment	
Immunogenicity*	Joao Pedras-Vasconcelos	Division of Biotechnology Review and Research III	
Immunogenicity*	Amy Rosenberg	Division of Biotechnology Review and Research III	

DS and DP Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	
Application Technical Lead	Maria-Teresa Gutierrez-Lugo	Division of Biotechnology Review and Research III	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=001181886 3, cn=Maria Teresa Gutierrez Lugo -S Date: 2015.12 23 13:06:57 -05'00'
Tertiary Reviewer	Susan Kirshner	Division of Biotechnology Review and Research III	Susan L. Kirshner -A Digitally signed by Susan L. Kirshner -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130019462 9, cn=Susan L. Kirshner -A Date: 2015.12.23 13:12:25 -05'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS

A. Submissions reviewed

Submission	Date Received	Review Completed (Yes/No)
Original submission	March 30, 2015	Yes
STN 761033/3	May 22, 2015	Yes
STN 761033/9	August 7, 2015	Yes
STN 761033/13	September 11, 2015	Yes
STN 761033/14	September 11, 2015	Yes
STN 761033/17	September 30, 2015	Yes
STN 761033/20	October 9, 2015	Yes
STN 761033/24	October 30, 2015	Yes
STN 761033/25	November 5, 2015	Yes
STN 761033/26	November 9, 2015	Yes
STN 761033/28	November 23, 2015	Yes
STN 761033/29	November 24, 2015	Yes
STN 761033/30	November 30, 2015	Yes
STN 761033/32	December 2, 2015	Yes
STN 761033/34	December 4, 2015	Yes
STN 761033/35	December 7, 2015	Yes
STN 761033/36	December 7, 2015	Yes
STN 761033/37	December 7, 2015	Yes

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	None
	III			3	Adequate	None
	V			1*	Adequate	None
	V			1	Adequate	None

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).

* Review of the MF focused on the media components relevant to this submission

3. CONSULTS:

None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761033 for Cinqair (reslizumab), manufactured by Teva Pharmaceuticals pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Cinqair is well controlled and leads to a product that is pure and potent. We recommend that Cinqair be approved for human use under the conditions specified in the package insert.

a. Benefit/Risk Considerations

Cinqair (reslilizumab) is an anti-interleukin 5 (anti-IL-5) monoclonal antibody intended for the treatment of asthma. The proposed dose is 3 mg/kg intravenously every four weeks. The proposed indication is to "reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids". Reslizumab is the second in the class of anti-IL-5 monoclonal antibody products. This class also includes mepolizumab, approved on November 4, 2015 as add-on maintenance treatment for patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

Asthma with eosinophilic phenotype is a serious condition associated with chronic morbidity, including frequent exacerbations. Reslizumab is intended for the treatment of asthma with eosinophilic phenotype. Review of the clinical data by OND determined that there is significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations in adults. However, evidence of efficacy and safety was less robust for subgroups with low enrollment, such as adolescents and African Americans. An increased risk of anaphylaxis, malignancy, or creatine phosphokinase (CPK) elevations was observed in patients treated with reslizumab during the asthma clinical trials.

OND determined the following risk/benefit: A physician who treated 1,000 patients with asthma with eosinophilic phenotype with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations, but could expect to manage 3 additional cases of anaphylaxis, 3 additional cases of malignancy, and 46 additional cases of CPK elevations.

Mepolizumab is an alternative anti-IL5 monoclonal antibody with comparable efficacy and a more favorable safety and tolerability profile. It is administered subcutaneously instead of intravenously. An increased risk of anaphylaxis, malignancy, or CPK elevations was not observed in the clinical trials for mepolizumab. Reslizumab represents a modest addition to the armamentarium and may prove useful for patients who cannot tolerate mepolizumab. Due to the risk of anaphylaxis, reslizumab is not suitable for home administration. Labelling should be sufficient to address the safety concerns.

The DS manufacturing process is well controlled and should consistently deliver DS of desired quality. However, (b) (4) DS control strategy can be implemented (b) (4) and (b) (4) may be conducted post licensure as Post Marketing Commitments (PMCs) because the applicant can consistently produce reslizumab DS that is safe, pure, and potent. The implementation (b) (4) will result better control of the overall process performance and improve the long term robustness of the process. Therefore, four PMCs related to the DS are included in the approval of this application (see section B, PMCs 1-4).

The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. However, confirmatory information for worst case microbiology studies and method improvements are needed to corroborate findings reported in the license application. In addition, the (b) (4) fill volume content recommendations in United States Pharmacopeia (USP) General Chapter <1151>. Because information provided in the license application show that the applicant can consistently produce DP that is safe, pure, and potent the confirmatory studies and reduction of fill volume may be conducted post licensure as PMCs. Therefore, four PMCs related to DP are included with the approval of this application (see section B, PMCs 5-8).

An additional PMC, related to both DS and DP is included with the approval of this application. This PMC is to evaluate, and if indicated revise, all the release and stability specifications after a sufficient number of lots of reslizumab are manufactured, usually around 30 lots. This is not an approvability issue because the current specifications are supported by clinical and current manufacturing experience and lead to a product that is safe, pure and potent. Revising the specifications after ~30 lots are manufactured will better reflect commercial manufacturing experience (see section B, PMCs 5 – 8).

b. Draft Action letter language

Manufacturing location:

- Drug substance – [redacted]
- Drug product – [redacted]
- Fill size and dosage form – 10 mg/ml, injection
- Dating period:
  - Drug product – 36 months; 2-8 ºC
  - Drug substance – 36 months; 2-8ºC
- Exempt from lot release

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

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

1. To improve the overall control strategy of the drug substance manufacturing process [redacted]
2. To implement a [redacted] in the drug substance manufacturing process.
3. To re-evaluate and tighten the [redacted] endotoxin acceptance criteria for the [redacted] samples after manufacturing 30 batches of reslizumab.
4. To establish a hold time limit for the intermediate [redacted] These hold times should be validated at scale to demonstrate that these [redacted] can be held under proposed worst-case conditions without compromising the microbial quality of the product.
5. To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab.

6. To requalify the microbial retention study at routine manufacturing/room temperature and submit the results in accordance with 21 CFR 601.12 by June 2016.

7. To requalify the dye ingress CCI test method with reslizumab 10 mL/20 mm vial under worst case challenge conditions using comprised positive controls with a breach size of ≤ (b) (4) µm and submit the data in accordance with 21 CFR 601.12 by April 2016.

8. To reduce the vial overfill to comply with compendial recommendations.

9. To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from at least thirty released lots of reslizumab drug substance and drug product.

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	Source or Origin	Risk	Control Strategy	Other
Identity	General CQA, intrinsic to the molecule. Major influencing factors include MCB/WCB genetic stability and production bioreactor.	Safety and Efficacy	Identity is tested at release (b) (4) [redacted] Controls also includ (b) (4) [redacted]	
Potency In vitro cell-based bioassay	Intrinsic to the molecule	Directly linked to efficacy In vitro potency is a measure of reslizumab's activity in inhibiting IL-5 mediated proliferation of (b) (4) [redacted] cell line	Drug substance release and stability testing	The proposed acceptance criteria for the release and stability specifications need to be revised to better reflect clinical and manufacturing experience. Awaiting response from the sponsor.
(b) (4) [redacted]		Potential impact on safety not fully understood	(b) (4) [redacted]	The proposed acceptance criteria for the release and stability specifications need to be revised to better reflect clinical and manufacturing experience. Awaiting response

(b) (4)		(b) (4)	from the sponsor.
	Safety and Efficacy Potential impact on safety and efficacy not fully understood		The proposed acceptance criteria for the release and stability specifications need to be revised to better reflect clinical and manufacturing experience. Awaiting response from the sponsor.
	Safety and Efficacy Potential impact on safety and efficacy not fully understood		
	Safety, especially immunogenicity		The proposed acceptance criteria for the release and stability specifications need to be revised to better reflect clinical and manufacturing experience. Awaiting response from the sponsor.
	Safety and		

(b) (4)	Efficacy Potential impact on safety and efficacy not fully understood	(b) (4)	
(b) (4)	Safety and efficacy	strategy	(b) (4)
(b) (4)	Safety and efficacy	Not currently part of DS control strategy (b) (4)	

B. Drug Substance: Reslizumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

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

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

CQA	Source or Origin	Risk	Control Strategy	Other
Appearance Color, clarity and visible particulate matter	General CQA Appearance might be impacted by the cell culture conditions, formulation process, but may also be an indicator of product degradation or other changes to the product.	Safety and efficacy	Appearance testing is part of DS release and stability testing. The acceptance criteria for DS at release and stability require that the DS is free of foreign particulates throughout the intended storage duration (b) (4)	
Protein Concentration	General CQA Protein concentration (b) (4)	Safety and efficacy	The protein content of reslizumab is controlled during (b) (4) testing and is monitored as part of DS release and stability specifications.	
pH	General CQA (b) (4) pH may be impacted on stability by breaches in container closure integrity or container closure leachables and by changes in the product.	Safety and efficacy	pH is assessed during (b) (4) testing as well as part of DS release and stability testing.	
Osmolality	General CQA (b) (4)	Safety	Osmolality is tested for reslizumab DS	

(b) (4)		(b) (4)	
	Safety		
	Safety		
	Safety		
	Immunogenicity and safety		

(b) (4)		(b) (4)	
	Immunogenicity and safety		
	Immunogenicity and safety		The proposed acceptance criteria for the release and stability specifications need to be revised to better reflect clinical and manufacturing experience. Awaiting response from the sponsor.
	Impact on safety (b) (4)		

(b) (4)	Safety	(b) (4)	
	Safety		

B. Drug Substance Quality Summary (cont.)

1. Description

Reslizumab is a humanized IgG4, κ monoclonal antibody produced in a NS0 cell line [redacted] at [redacted] scale. The reslizumab DS manufacturing process consists of [redacted] Drug substance is [redacted] stored at 2-8 C. For additional information see Appendix A and Appendix B.

2. Mechanism of action

Reslizumsab binds to soluble IL5 and blocks IL5 binding to the IL5 receptor alpha on eosinophils and other cells expressing the IL5 receptor. IL5 is a soluble dimer and is not expressed on cell surfaces. Therefore, Fc effector function is not a part of the reslizumab MOA. For additional information see Appendix A.

3. Potency Assay

Potency of reslizumab is defined as the percent activity relative to a reslizumab reference standard. The potency assay is a cell-based potency assay using [redacted] cell line, that expresses the IL-5 receptor. The biological activity of reslizumab is measured by inhibition of cell growth induced by IL-5 in a dose-dependent manner. Cell viability is measured [redacted] For additional information see Appendix A.

4. Reference material(s)

The current reference standard program for reslizumab comprises of a single reference standard, Reference Standard batch 202709ARS is used for release and stability testing.

The primary reference standard was developed from DS batch 202709 manufactured in 2011. This DS batch was manufactured by the commercial manufacturing process and it is representative of phase 3 asthma trials. Protocols for the qualification of a two-tier reference standard system were provided in the application and found appropriate. (b) (4) For additional information see Appendix A.

5. Critical starting materials or intermediates

Master Cell Bank MCB (b) (4) was derived (b) (4) (b) (4) Working Cell Bank WCB (b) (4) was derived (b) (4) MCB (b) (4) and WCB (b) (4) were properly qualified. A protocol for qualification of future cell banks was reviewed as part of the BLA and found acceptable. For additional information see Appendix A.

6. Manufacturing process summary

(b) (4)

Reslizumab is manufactured (b) (4)
Microbial quality of the DS manufacturing process is well controlled (b) (4)

The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with (b) (4) and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents. For additional information see Appendix A and Appendix B.

7. Container closure

The drug substance container closure (CCS) is [redacted] (b) (4) suitable for reslizumab manufacturing based on extractable leachable studies, and stability data. These data support that CCS is safe for use and maintain its integrity during shipping. For additional information see Appendix A and Appendix B.

8. Dating period and storage conditions:

The dating period for reslizumab drug substance is 36 months at 2-8 ºC based on real time stability data from three process validation batches. The dating period is further supported by accelerated and stress stability data and supporting real time stability data from reslizumab DS lots manufactured by the commercial process For additional information see Appendix A.

C. Drug Product: Cinqair Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information on the characterization of Cinqair see Appendix A for the Drug Substance and Drug Product Quality Technical Report: OBP Assessment and Appendix B Drug Substance and Drug Product Microbiology Review: Division of Microbiology Assessment.

Table 3: Cinqair CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Origin	Risk	Control Strategy	Other
Protein content	General CQA Protein concentration (b) (4) [redacted]	Safety and Efficacy	Reslizumab content is controlled during (b) (4) [redacted] testing and as part of the DP release and stability specifications.	
Sterility and container closure integrity	Contamination. Sterility could be compromised by contaminants introduced throughout drug product manufacturing or through a Container closure integrity failure. Container closure integrity is a sterility assurance CQA.	Safety	Sterility is monitored as part of DP lot release and container closure is part of stability testing.	
Endotoxin	Contaminant that could be introduced throughout drug product manufacturing (b) (4) [redacted]	Safety	Controlled (b) (4) [redacted] as part of DP release specifications (b) (4) [redacted]	
Sub-visible particulate (SVP)	SVP could form throughout manufacturing and during DP storage.	Safety (capillary occlusion) and Immunogenicity	Sub-visible particles (b) (4) [redacted] are monitored at DP release.	(b) (4) [redacted] Awaiting response from

				the sponsor.
Visual Appearance	General CQA Appearance might be impacted by the formulation, but may also be an indicator of product degradation or other changes to the product.	Safety and efficacy	Appearance is tested (b) (4) and included in DP release and stability specifications. Acceptance criteria are established for clarity, color, and visible particulate matter. 100% manual inspection is performed for each DP batch. Reslizumab contains visible proteinaceous particulates. The product is administered by IV infusion. The infusion set includes an in-line filter.	Reslizumab contains visible proteinaceous particulates. The acceptance criteria reflect the nature of the acceptable particles. However, the acceptance criteria should be revised to indicate that the product is free from foreign material. Awaiting response from the sponsor.
Extractable Volume	General CQ (b) (4)	Safety and efficacy (low extractable volume)	Fill volume is part of the DP release specifications. Fill weight is controlled (b) (4) .	The release acceptance criteria for extractable volume should be revised to reduce the overfill. This will be a PMC.
pH	General CQA (b) (4) pH may be impacted on stability by breaches in container closure integrity or container closure	Safety and efficacy	pH is included during (b) (4) (b) (4) testing as well as part of DP release and stability specifications.	

	leachables or changes in the product.			
Osmolality	General CQA (b) (4)	Safety	Osmolality is tested during (b) (4) DP processing and at release and stability.	
Leachables	Leachables could potentially be introduced by any product contact equipment, container closure and consumables.	Safety	Supported by leachables and extractables risk assessments for the product contact materials used in DP manufacture and storage and by stability studies.	

Cinqair Drug Product Quality Summary (Cont.)

1. Potency and Strength:

Potency is defined as the percent activity relative to reslizumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Cinqair will be available in an 10 mg/ml strength.

2. Summary of Product Design

Cinqair is presented in a single-dose glass vial containing 10 mg/ml of reslizumab. More than one vial may be needed to achieve the recommended dose of 3 mg/kg for a given patient depending of body weight. Cinqair is administered by intravenous infusion after dilution with saline, USP. The infusion setting includes an in-line filter. For additional information see Appendix A.

3. List of Excipients

Each mL contains glacial acetic acid (0.12 mg), sodium acetate trihydrate (2.45 mg), and sucrose (70mg). For additional information see Appendix A.

4. Reference material(s),

The same reference materials are used for DS and DP. Refer to DS section. For additional information see Appendix A.

5. Manufacturing process summary

The drug product manufacturing process consists of (b) (4) 100% visual inspection, and packaging of vials.

Critical parameters selected for routine monitoring relate to (b) (4) The control strategy includes (b) (4) testing and release testing of final DP. Appropriate (b) (4) controls for microbial limits and sterility assurance are incorporated into the manufacturing process. For additional information see Appendix A and Appendix B.

6. Container closure

Cinqair is supplied as 10 ml vial containing 10 ml of reslizumab at the concentration of 10 mg/ml (100 mg). The container closure system consist of a 10 ml Type I clear borosilicate glass tubing vial, capped with a 20 mm stopper with (b) (4) a 20 mm aluminum crimp seal with royal blue flip-off cap. For additional information see Appendix A and Appendix B.

7. Dating period and storage conditions:

The dating period for drug substance is 36 months at 5 ± 3ºC.

8. List of co-packaged components: not applicable.

D. Novel Approaches/Precedents: N/A

E. Any Special Product Quality Labeling Recommendations

- Protect from light
- Do not freeze
- Do not shake

F. Establishment Information

OVERALL RECOMMENDATION: Pending				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
DS production (b) (4) DS release and stability testing, DS storage, and MCB and WCB cell bank storage	(b) (4)	FEI: (b) (4)	7 item 483. Satisfactory response to 483 observations. Final inspection classification VAI	Approve
MCB and WCB cell bank production and storage		FEI: (b) (4)	N/A	Not applicable
Drug substance and finished drug product release and stability testing		FEI: (b) (4)	No 483 after PAI and GPM inspection.	Pending
Release and stability testing: (b) (4) (b) (4)	Teva Pharmaceutical Works Private Limited Company Site 1, Pallagi St. 13 Debrecen, 4042, Hungary	FEI: 3002806524	N/A	Approved based on profile
Drug substance release testing: (b) (4) (b) (4)	(b) (4)	FEI: (b) (4)	N/A	Facility approved based

(b) (4)	(b) (4)			on profile
Drug substance release testing: (b) (4)		FEI: (b) (4)	N/A	Facility approved based on profile
(b) (4)		FEI: (b) (4)	N/A	Facility approved based on profile

DRUG PRODUCT

FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
(b) (4) Labeling and Secondary Packaging of finished product Release& stability testing	(b) (4)	(b) (4)	N/A	Facility approved based on district recommendation

of finished product responsibilities				
Release & stability testing of finished product	(b) (4)	(b) (4)	See DS section	Approve
Release & stability testing of finished product		(b) (4)	See DS section	Approve
Release & stability testing of finished product: (Potency Bioassay)	Teva Pharmaceutical Works, plc. Pallagi Street 13 H-4042 Debrecen Hungary	3002806524	See DS section	Approve

G. Facilities

The subject BLA proposes manufacture and testing of reslizumab drug substance and drug product at the following facilities.

[redacted] is responsible for drug substance manufacture and [redacted] release and stability testing of the DS. [redacted] also responsible for release and stability testing of the DP. A seven-item Form FDA 483 was issued to the firm at the end of the inspection [redacted] The firm adequately addressed observations raised by the FDA 483. The final classification was VAI.

Cell banking operations will occur [redacted]

[redacted] is responsible for DP manufacture and release and stability testing of DP. This facility was approved based on district recommendation.

Additional testing operations for the DS and DP will occur at [redacted] Teva Pharmaceutical Works Private Limited, Debrecen, Hungary (FEI 3006067169), [redacted] A PAI inspection [redacted] was conducted [redacted] No FDA 483 was issued. An expedited PAI review completed and approved for profile CTL. The EIR package will be submitted to DIA for a full review once completed. The rest of the facilities were approved based on profile.

For additional establishment information see Appendix C.

H. Lifecycle Knowledge Management

a. Drug Substance

a. Protocols approved:
   i. Annual stability protocol
   ii. Qualification of new working reference standard
   iii. Qualification of new working cell banks

iv. Chromatography (b) (4)

b. Outstanding review issues/residual risk:
   i. Pending IRs to revise specifications for DS to better reflect clinical and manufacturing experience
c. Future inspection points to consider: none

b. Drug Product

c. Protocols approved:
   i. Annual stability protocol
   i. Outstanding review issues/residual risk:

   Pending IRs to revise specifications for DS to better reflect clinical and manufacturing experience.

d. Future inspection points to consider: none

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_____		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 team)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____			X	
Quality Considerations					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			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	

APPENDIX A

DRUG SUBSTANCE AND DRUG PRODUCT QUALITY REVIEW: OBP

Reviewers: Ramesh Potla (DS) and Tracy Denison (DP)

Division of Review and Research III, OBP, OPQ

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

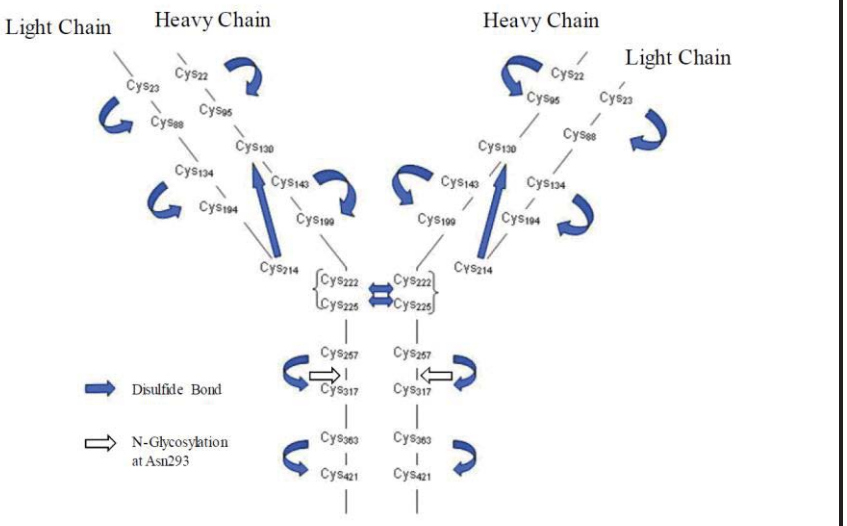
Unless explicitly indicated, all figures and tables in this review are copied directly from the BLA submission or from information request responses.

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

Reslizumab (CEP-38072) is a recombinant, humanized IgG_4, κ monoclonal antibody to the human interleukin-5 (anti-IL-5 MAb). Reslizumab contains the complementary determining regions (CDRs) of the original rat antihuman antibody 39D10 grafted onto a human framework. It is composed of two light chains and two heavy chains linked by 12 intra-chain and 4 inter-chain disulfide bonds. (b) (4) N-linked oligosaccharides of reslizumab are (b) (4) derived from NS0 cell lines. The predicted molecular mass is 146.8 kDa. The schematic diagram of reslizumab is shown below:

Figure 1: Structural Representation of Reslizumab Disulfide Bond Linkage



The predicted amino acid sequence of reslizumab is provided below:

Table 1: Theoretical Amino Acid Sequence for Reslizumab

Heavy Chain
(b) (4)
Light Chain
(b) (4)

Reviewer Comment: (b) (4)

3.2.S.1.3 General Properties

Reslizumab is a humanized IgG_4, κ monoclonal antibody produced in a NS0 cell line. Reslizumab binds to soluble circulating human IL-5 and prevents its binding to the IL-5 receptor on eosinophils, thereby inhibiting their proliferation and activation. The drug substance (DS) contains reslizumab at (b) (4) mg/mL concentration, (b) (4) The properties of reslizumab are provided in the table below:

Table 1: Reslizumab Drug Substance General Properties

Property	Description
Appearance Clarity and degree of opalescence of a liquid	Clear to slightly hazy/opalescent solution
Appearance Degree of coloration	Colorless to slightly yellow/yellow solution
Protein type	Human IgG4, kappa
Amino acid sequence	Section 3.2.S.1.2, Table 1
Molecular mass (theoretical)	146,776 Da (b) (4) (b) (4)
Glycosylation	N-Glycosylated at Asn293 (b) (4) (b) (4) (b) (4)
UV Extinction coefficient at the wavelength of A (b) (4)	
pH at (b) (4) °C	
Protein concentration	
pI of main peak	
Osmolality	
Thermodynamics	
Sedimentation coefficient	
Disulfide linkage	16 disulfide bonds
Biological activity	Inhibition of proliferation of (b) (4) cells Potency: (b) (4) % relative potency

Reviewer Comment: (b) (4) *The recommended storage conditions for both DS and DP are 5±3 °C.*

Reslizumab's Mechanism of Action:

Reslizumab is a humanized IgG4 monoclonal antibody that binds to and neutralizes human IL-5. IL-5 mediates the proliferation, activation, and survival of target eosinophil cells. The mechanism of action for reslizumab is achieved by blocking IL-5 binding capacity to its specific receptor. Using a combination of synthetic peptide mapping and site-directed mutagenesis studies, it is determined that reslizumab recognizes a tetrapeptide with amino acid residues 89 – 92 (E89, R90, R91, and R92) as the minimal epitope on human IL-5. In addition, results from amino acid substitution studies showed that an additional three amino acid residues (K85, G87, and N94) located in the vicinity of the minimal epitope region also impact the binding of reslizumab to IL-5 (Zhang et al, 1999). Three (E89, R90, and R91) out of 4 amino acid residues located in the minimal epitope region of human IL-5 are also confirmed as key residues for the interaction of IL-5 with human IL-5 receptor α complex (Graber, 1995; Tavernier, 1995; and Patino et al, 2011). Overall, the provided information demonstrate that reslizumab neutralizes soluble IL-5 and prevents this cytokine from binding to IL-5 receptor α, thereby preventing the activation of eosinophils and their consequent mobilization into the bronchial airspace. See Figures 1 and 2 below for schematic diagram(s) on reslizumab's mechanism of action.

Figure 1: Reslizumab Mechanism of Action

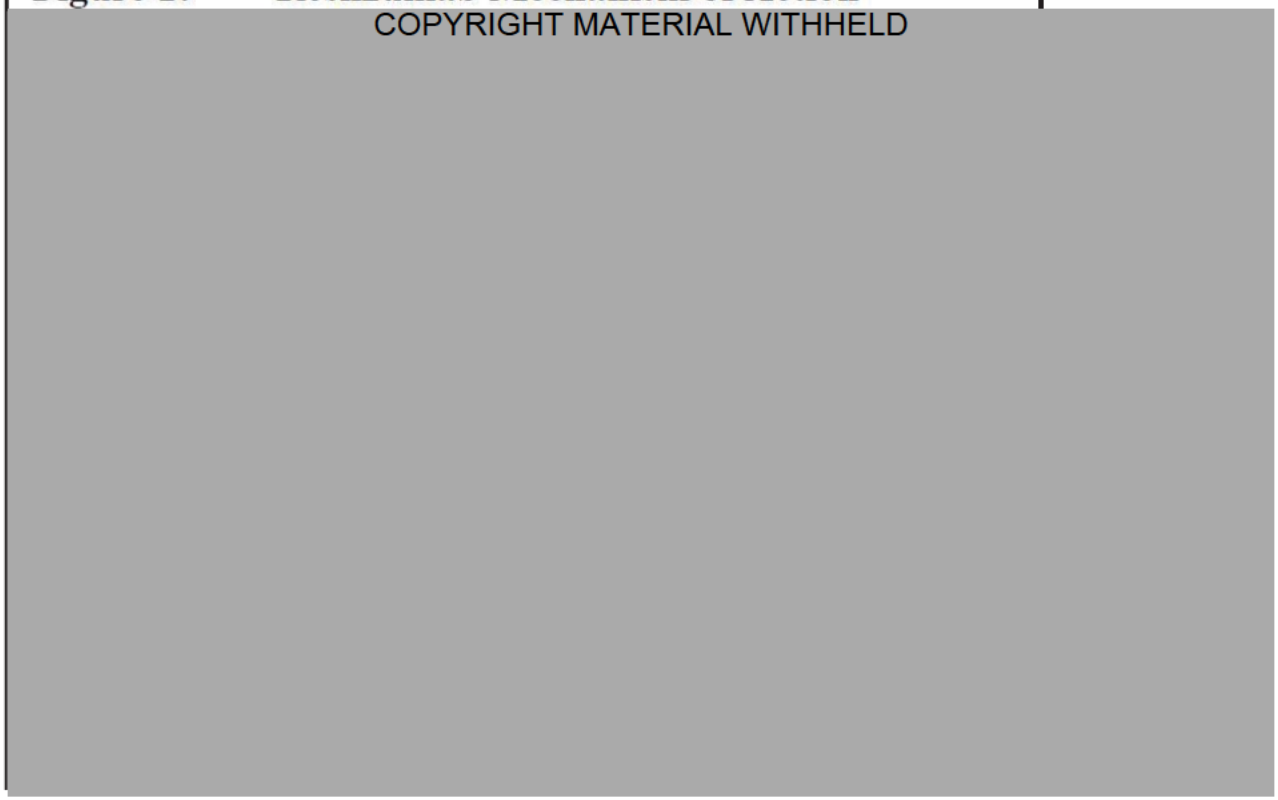


Figure 2: Human IL-5 Interacting with IL-5 Receptor α at Residues E^{89}, R^{90}, and R^{91}

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Reslizumab DS is manufactured [redacted] (b) (4) for Teva Pharmaceuticals. The manufacturing, testing and storage sites for reslizumab DS are shown in the table below:

Table 1: Manufacturers and Contractors for Reslizumab Drug Substance

Name and Address of Site	Activities Performed	Status Facility Establishment Identifier (FEI) Number Data Universal Numbering System (DUNS) Number
[redacted] (b) (4)		

(b) (4)

3.2.P. DRUG PRODUCT

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

Reslizumab is a humanized anti-interleukin-5 IgG4 antibody. The proposed indication is for use by adolescents and adults with asthma and elevated blood eosinophil levels who are not well-controlled by inhaled corticosteroids. For this subset of asthma patients it is intended to reduce exacerbations, relieve symptoms, and improve lung function. It is produced by recombinant DNA technology expressed in murine NS0 cells. The expected mechanism of action is to bind to interleukin-5 (IL-5) and prevent it from binding to the IL-5 receptor. The drug product presentation of reslizumab is a colorless to slightly yellow aqueous solution supplied in 10 ml and containing 100 mg of reslizumab, which is a concentration of 10 mg/ml. It is provided sterile and without preservatives, and is diluted with saline prior to infusion. It is provided in a Type I clear, borosilicate glass vial. The closure includes a (b) (4) rubber stopper which is sealed over with an aluminum flip-off seal. Each vial is intended for single use only and remaining drug product must be discarded after use. Patients are to be dosed at 3 mg/kg every four weeks.

3.2.P.2 Pharmaceutical Development

The following section reviews aspects of the pharmaceutical development of the reslizumab drug product.

3.2.P.2.1 Components of the Drug Product

The following table lists the components in the reslizumab drug product.

Table 1: Composition of the Reslizumab Drug Product

Component	Amount per mL	Reference to Standard	Function
Reslizumab (CEP-38072) protein	10 mg	In house specifications	Drug substance
Sucrose (b) (4)	70 mg	NF/Ph. Eur./JP	(b) (4)
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	
(b) (4)			

3.2.P.2.1.1 Drug Substance

[redacted]

Drug product reslizumab concentration is 10 mg/ml.

3.2.P.2.1.2 Excipients

The excipients for reslizumab include the following components listed in the following table, with respective information for grade and formulation function.

Table 1: [redacted]

Component	Amount per mL	Reference to Standard	Function
Sucrose	70 mg	NF/Ph. Eur./JP	[redacted]
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	

[redacted]

Reviewer's Comment: The components of the drug product formulation are appropriate. The active ingredient will be controlled as reviewed later and other components of the formulation are held to compendial standards generally recognized in the United States. Every component has a defined purpose.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

47 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

The sponsor uses six analytical methods that are uniquely performed on drug product and occur at its manufacturing site . The analytical methods tested include osmolality, volume in container, endotoxin, sterility subvisible particulate matter, and bioburden. These six methods are performed following the compendia described in the following table.

Analytical Method	Compendial Compliance
Osmolality	Ph. Eur. 2.2.35 "Osmolality" and USP <785>
Volume in container	USP <1>
Endotoxin	Ph. Eur. 2.6.14 "Bacterial Endotoxins" and USP <85>
Sterility (b) (4)	Ph. Eur. 2.6.1 "Sterility" and USP <71>
Subvisible particulate matter	Ph. Eur. 2.9.19 "Particulate Contamination: Sub-visible Particles" and USP <788>
Bioburden	USP <61> "Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests." and Ph. Eur. 2.6.12 "Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests."

The sponsor indicated that verification of some compendial methods was performed, as shown in the table below. Those methods that are performed (b) (4) and were qualified based (b) (4) internal procedure with reports provided as shown. This information was provided to FDA on December 2, 2015 in response to an information request.

Table 1: Provided Reports

Analytical Method	Validation/Verification Report
Appearance: Color and Clarity	(b) (4) Report USPO-6955
Appearance: Visible Particles	Report USPO-7856
Osmolality[1]	Report USPO-5810
pH	Report USPO-REC-437
Sub-visible particulate matter USP<788>	N/A
Volume in Container USP<1>	N/A

[1] Osmolality was verified for drug substance testing (b) (4) Osmolarity was not verified for drug product testing (b) (4) Per their internal procedures, (b) (4) does not perform verification for routine compendial methods.
N/A=Not applicable

Reviewer's Comment: (b) (4) *The use of compendial methods is appropriate and those methods were qualified by respective organizations following their internal procedures or USP guidance. The Division of Microbiology Assessment will evaluate the adequacy of the sterility, bioburden, and endotoxin assays.*

(b) (4)

5 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The three process validation batches were used as primary stability batches to support stability. These lots have been subject to stability testing under the following conditions and durations.

- Long term - (b) (4) (36 months stability data currently available)
- Accelerated - (b) (4) (12 months stability data available)
- Stress - (b) (4) (6 months stability data available)

The following table describes further information regarding these primary stability batches.

Table 1: Summary Information for Reslizumab Drug Product Primary Stability Batches

Lot number	11-002802	11-002803	11-002804
Strength	100 mg/vial, 10 mg/mL	100 mg/vial, 10 mg/mL	100 mg/vial, 10 mg/mL
Use	Stability, Phase 3 clinical (BREATH program[1]), and process validation	Stability, Phase 1 (C38072/1107) and 3 clinical (BREATH program[1]) and process validation	Phase 3 clinical (C38072/3085), stability, and process validation
Drug Product Batch Size	(b) (4)		
Drug substance lot(s)	89991 + 202709	202709	204006
Date of Drug Substance manufacture	08 Nov 2008 + 08 Dec 2010	08 Dec 2010	13 Dec 2010
Site of manufacture	(b) (4)		
Date of Fill Finish			
Package	10 mL clear glass vial, with 20 mm rubber stopper and aluminum seal	10 mL clear glass vial, with 20 mm rubber stopper and aluminum seal	10 mL clear glass vial, with 20 mm rubber stopper and aluminum seal
Intended Storage Conditions (b) (4) (b) (4)	2 - 8 °C	2 - 8 °C	2 - 8 °C
Accelerated and Stressed Storage Condition (b) (4) (b) (4)	(b) (4) (Studies competed)	(Studies competed)	(Studies competed)
Study start date	28 Oct 2011	28 Oct 2011	18 Nov 2011
Amount of stability data at 2-8°C (months)	36 (Study Ongoing)	36 (Study Ongoing)	36 (Study Ongoing)

[1]The BREATH program is comprised of clinical studies C38072/3081, C38072/3082, C38072/3083, C38072/3084 and C38072/3085

The sponsor is proposing a labeled shelf-life of 36 months when stored at 2-8 °C. The data currently support this shelf life with the three process validation lots tested under real-time conditions out to 36 months. The accelerated stability testing indicates the product is reasonably (b) (4) and other supporting real-time stability data suggest the product

may be stable at (b) (4) years. (b) (4)

Reviewer Comment: Generally the stability data are supportive of the 36-month shelf life. At least three lots indicated a real-time stability out to 36 or more months. The stability data from lots during development are also supportive of the proposed shelf life. The product was also mostly stable for several months at accelerated and stressed stability testing. For these reasons a proposed 36-month shelf life at 2-8 °C is acceptable. An IR to the sponsor will be sent to clarify if the sponsor intends to use their stability protocol (b) (4).

3.2.P.8.2 Post-Approval Stability Commitment

The sponsor has committed to the following Post-Approval Stability Protocol, (b) (4)

(b) (4)

Reviewer's Comment: Overall, the stability protocol is appropriate as it incorporates the same testing used for release and follows general stability guidelines However, the stability protocol should be revised to include (b) (4) testing. An IR will be sent to the sponsor to address this issue In addition, the sponsor was asked to clarify their commitment to provide updated stability data from their ongoing stability commitment as part of their annual reporting. Any further information regarding this commitment provided by the sponsor will be included in an addendum to this review.

3.2.P.8.3 Stability Data

Several lots of reslizumab drug product have been tested on stability. The permutations of stability conditions tested include vials stored (b) (4) for real-time, accelerated, and stressed conditions. A total of six lots have been provided that have at least 36 months of real-time testing to support the proposed shelf life. The stressed or accelerated conditions were usually tested in the range of 6-24 months. The following table indicates the data provided in the BLA submission for different drug product batches and the purposes of those batches.

Table 1: Stability Data for Reslizumab Drug Product

Lot Number	Site	Purpose	Data Provided (Months)	Storage Conditions/Configuration
11-002802	(b) (4)	Stability, Phase 3 clinical (BREATH program), and process validation	36	2-8°C (b) (4)
			36	2-8°C
			12	25°C/60% RH (b) (4)
			12	25°C/60% RH
			6	40°C/75% RH
			6	40°C/75% RH
11-002803		Stability, Phase 1 (C38072/1107) and 3 clinical (BREATH program) and process validation	36	2-8°C (b) (4)
			36	2-8°C
			12	25°C/60% RH (b) (4)
			12	25°C/60% RH
			6	40°C/75% RH
			6	40°C/75% RH
11-002804		Phase 3 clinical (C38072/3085), stability, and process validation	36	2-8°C (b) (4)
			36	2-8°C
			12	25°C/60% RH (b) (4)
			12	25°C/60% RH
			6	40°C/75% RH
			6	40°C/75% RH
12358		Stability, process validation	12	2-8°C (b) (4)
			12	2-8°C
			12	25°C/60% RH (b) (4)
			12	25°C/60% RH
			6	40°C/75% RH
			8	40°C/75% RH
12-000792		Stability, Phase 3 clinical	18	2-8°C (b) (4)

Lot Number	Site	Purpose	Data Provided (Months)	Storage Conditions/Configuration
	(b) (4)	(C38072/3085 and Compassionate Use/Expanded access)	18	2-8°C/ (b) (4)
			12	25°C/60% RH / (b) (4)
			12	25°C/60% RH /
			6	40°C/75% RH/
			6	40°C/75% RH /
11-000701		Stability, development and Phase 3 clinical (BREATH program)	36	2-8°C / (b) (4)
10-000862		Stability, Phase 1 (C38072/1102) and 3 clinical (BREATH program)	36	2-8°C /
10-001036 (10GG003A503)		Stability, Phase 2 (5-0004) and Phase 3 clinical (BREATH program)	48	2-8°C/
			48	2-8°C/
			24	25°C/60% RH (b) (4)
			24	25°C/60% RH
			6	40°C/75% RH
			6	40°C/75% RH

The product was stable at real-time storage conditions generally for the specifications that were in place at the time of testing. A representative sample of real-time testing for one of the process validation lots is shown in the following tables.

Stability Data for Reslizumab Drug Product, Process Validation Lot 11-002802 (2-8°C- (b) (4)

Assay	Specification ((b) (4) USPO-6663/4.0[5]) ((b) (4) QCMD-918503)	Time (months)											
		0	1	3	6	9	12	18	24	30[5]	36	48	60
(b) (4)													

Assay	Time (months)												
	Specification ((b) (4) USPO-6663/4.0[5]) ((b) (4) QCMD-918503)	0	1	3	6	9	12	18	24	30[5]	36	48	60
(b) (4)													

Assay	Time (months)												
	Specification ((b) (4) USPO-6663/4.0[5]) ((b) (4) QCMD-918503)	0	1	3	6	9	12	18	24	30[5]	36	48	60
(b) (4)													

Assay	Time (months)												
	Specification (b) (4) USPO-6663/4.0[5]) ((b) (4) QCMD-918503)	0	1	3	6	9	12	18	24	30[5]	36	48	60
													(b) (4)

Reviewer Comment: The reslizumab drug product is stable under the recommended storage conditions of 2-8 °C out to 36 months for all the process validation lots. (b) (4) . *Overall, the real-time stability data support the proposed shelf life of 36 months.*

A representative example of stressed stability testing is provided for the same process validation discussed above in the table below.

Stability Data for Reslizumab Drug Product, Process Validation Lot 11-002802 (40°C/ 75% RH (b) (4)

Assay	Specification ((b) (4) USPO-6323/3.0) ((b) (4) QCMD-918503)	Time (months)			
		0	1	3	6
(b) (4)					

Assay	Specification (USPO-6323/3.0)	Time (months)			
		0	1	3	6
(b) (4)					

(b) (4)

Reviewer's Comment: Even under the stressed conditions of 40 °C/75% relative humidity the drug product is resilient to degradation and is compliant with many of the specifications.

(b) (4)

The potency was still maintained at 6 months of accelerated conditions.

The results of photostability testing were reported in Section *3.2.P.2.4. Container Closure*.

(b) (4)

The stability of product under shipping conditions was provided and reviewed under section *3.2.P.3.5 Process Validation* under the section of Shipping Qualification.

(b) (4)

Reviewer Comment: Overall, the stability testing data is sufficient and adequate to support the proposed shelf life of 36 months for drug product. Reslizumab drug product is quite stable for weeks to months at stressed storage conditions (b) (4) *and the data suggest the product will be stable under normal use and handling as described on the label. The sponsor updated the available stability data in a response to an IR dated December 2, 2015 and the new data submitted then also supports the overall stability and proposed expiry of the product.*

3.2.A Appendices Table of Contents

3.2.A.1 Facilities and Equipment

Reviewer Comment: *Review of information provided on the facilities and equipment is deferred to DMA/DIA review team.*

3.2.A.2 Adventitious Agents Safety Evaluation

The overall control strategy for ensuring adventitious agent safety is comprised of the following elements:

50 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDIX B

DRUG SUBSTANCE AND DRUG PRODUCT QUALITY REVIEW: DMA

Reviewers: Bo Chi, Ph.D. (DS) and Lakshmi Rani Narasimhan, Ph.D. (DP)

Teal Lead: Patricia Hughes, Ph.D., Acting Branch Chief

DMA/Branch IV, OPF, OPQ

Recommendation: The drug substance part of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following two post-market commitments:

Re-evaluate and tighten the (b) (4) endotoxin acceptance criteria (b) (4) samples after manufacturing 30 batches of reslizumab.

Establish a hold time limit for the intermediate (b) (4) These hold times should be validated at scale to demonstrate that these (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.

The committed updates for the (b) (4) bioburden and endotoxin limits in the BLA will be verified in the addendum of the integrated review memo.

Review Summary

Teva submitted this Biologics License Application (BLA) for reslizumab for relieve symptoms and improve lung function in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. The drug substance (DS) is manufactured (b) (4) The drug product (DP) is manufactured (b) (4) The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of reslizumab drug substance from microbiology perspective.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Reslizumab is a humanized monoclonal antibody to interleukin-5 (IL-5). Il-5 is a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. Reslizumab binds to IL-5 and prevents its binding to the IL-5 receptor, therefore reduces circulating and tissue eosinophils. The drug substance contains (b) (4) mg/mL reslizumab (b) (4) Reslizumab is produced in the murine myeloma NS0 cell line (b) (4)

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Drug substance manufacture and storage, drug substance (b) (4) testing, drug substance and drug product release and stability testing

(b) (4)

FEI: (b) (4)

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)

(b) (4)

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

DRUG PRODUCT

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

Requalify the dye ingress CCI test method with reslizumab 10 mL/20 mm vial under worst case challenging conditions using comprised positive controls with a breach size of ≤ (b) (4) µm and submit the data by April 2016.

The performed microbial retention study (b) (4) did not consider the effect of worst case or manufacturing temperature on the reslizumab product and the challenge organism. Please requalify the microbial retention study at routine manufacturing temperature and submit the results by June 2016.

SUMMARY:

Teva Branded Pharmaceutical Products R&D, Inc. (Teva) has submitted a new biologics license application, BLA 761033 to license the use of reslizumab. Drug substance is manufactured (b) (4) and drug product is manufactured (b) (4)

The application was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 and Module 3. In response to IR dated October 19, 2015, a Letter of authorization (LOA) for (b) (4) Type V DMF (b) (4) to reference the information regarding environmental monitoring (b) (4) was provided.

INTRODUCTION

Reslizumab drug product (DP) is manufactured (b) (4) DP is also referred as CEP-38072 in the BLA application. The recommended dose of DP is 3.0 mg/kg every 4 weeks, provided as an intravenous infusion diluted in sterile 0.9% sodium solution.

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	May 22, 2015	Amendment
0009	August 07, 2015	Amendment
0013	September 11, 2015	Amendment
0024	October 30, 2015	Amendment
0025	November 05, 2015	Amendment
0026	November 09, 2015	Amendment
0029	November 24, 2015	Amendment
0032	December 02, 2015	Amendment

ASSESSMENTS:

3.2.P DRUG PRODUCT

Reslizumab drug product

DP manufacturing process include (b) (4) No new excipients are introduced.

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

DP is a preservative-free, sterile, colorless to slightly yellow aqueous solution presented as 100 mg in a single-use 10 mL glass vial. DP is diluted in sterile 0.9% sodium chloride solution prior to infusion. The composition of DP provided in Table 1 is reproduced below.

Table 1: Composition of the Reslizumab Drug Product

Component	Amount per mL	Reference to Standard	Function
Reslizumab (CEP-38072) protein	10 mg	In house specifications	Drug substance
Sucrose (b) (4)	70 mg	NF/Ph. Eur./JP	(b) (4)
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	
(b) (4)			

Reviewer's comments: The pH release specification for reslizumab drug product is 5.5 (b) (4)

Container closure system

DP solution is packaged in a Type I clear, borosilicate 10 mL glass vial, stoppered with a (b) (4) rubber serum stopper and sealed with aluminum flip-off seal.

Satisfactory

Labeling

FDA question (May 11, 2015): The proposed labeling claims that drug product diluted in normal saline may be stored refrigerated at 2- 8°C (36- 46°F) or at room temperature up to 25ºC (77ºF), protected from light for up to 16 hours. Please submit microbiological studies to support the 16 hour storage time at 2- 8°C or at room temperature up to 25ºC. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution storage period is not more than 4 hours at 2-8°C.

Firm's Response in amendment dated May 22, 2015 in sequence # 0003: The microbiological data supporting the storage conditions of the diluted drug product will be submitted by the end of July 2015.

Firm's Response in amendment dated August 07, 2015 in sequence # 0009: Reslizumab, lot 12358 was used for the microbial challenge study. Prior to the challenge study, a recovery method validation was performed using DP, (b) (4) to demonstrate that the DP is not inhibitory to the challenge organisms. DP IV solutions (b) (4) were prepared by diluting the DP (10 mg/mL) in 0.9% sodium chloride in 50 mL IV bags. The infusion bags were inoculated with ≤ (b) (4) CFU/mL of USP <51> challenge organisms: *S.aureus* (ATCC 6538), *P. aeruginosa* (ATCC 9027), *E. coli* (ATCC 8739), *C. albicans* (ATCC 10231) and *A. brasiliensis* (ATCC 16404) and common skin flora associated with hospital environments: *Streptococcus pyogenes* (ATCC 19615), *Staphylococcus epidermidis* (ATCC CRM-12228) and *Proprionibacterium acnes* (ATCC 6919). The bags were stored at 2-8°C and room temperature (20-25°C) and sampled at 0, 4, 8, 16, 24, and 32 hour time points and the growth was enumerated by plate count. Inoculum controls were prepared at T_0 to verify the inoculum concentration. Acceptable criteria for support of storage conditions are 'no growth', which is interpreted as not more than '(b) (4) $\log_{10}$ increase from the previous time point'.

Reviewer's comments: Tables showing the challenge organisms' log recovery and log increase/decrease from previous time point for the tested concentrations, (b) (4) at both storage temperatures were included in the report. The data indicated that the growth was less than (b) (4) Log_{10} for all tested challenge organisms demonstrating that (b) (4) DP preparations in saline will not promote microbial growth for up to (b) (4) hours when stored at 2°-8°C or 20°-25°C.

The submitted microbiological challenge study data support the proposed labeling claim for the storage of diluted drug product for up to 16 hours under refrigeration at 2-8°C or at room temperature up to 25ºC.

Satisfactory

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

Microbiological Attributes

(b) (4)

DP is tested for sterility and bacterial endotoxins (NMT (b) (4) EU/mg) at release.

Reviewer's comments: Release DP endotoxin specification was tightened to (b) (4) EU/mg to provide a safety factor.

Container Closure Integrity Test

Microbial Ingress Method

CCS of DP was subjected to an integrity test following container closure operational qualification (CCOQ). The microbial ingress CCI test was performed on the (b) (4) vials.

(b) (4)

(b) (4)

BLA STN 761033
Drug Product Quality Review

Reslizumab

Teva Pharmaceuticals

Tracy A. Denison, PhD
Maria Teresa Gutierrez, PhD
Division of Biotechnology Review and Research III

OBP CMC Review Data Sheet

1. **BLA#:** STN 761033

2. **REVIEW DATE:** Dec 16, 2015

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Kathleen Donohue
Pharm/Tox: Carol Galvis
Product Quality Team: Tracy Denison (drug product), Ramesh Potla (drug substance),
OBP Immunogenicity: Joao Pedras-Vasconcelos
BMT or Facilities: Thuy Nguyen
Clinical Pharmacology: Yunzao Ren
Statistics: Lan Zeng
OBP Labeling: Jibril Abdus-Samad
RPM: Colette Jackson

4. **MAJOR GRMP DEADLINES**
Filing Meeting: May 11, 2015
Mid-Cycle Meeting: September 8, 2015
Wrap-Up Meeting: February 4, 2016
Primary Review Due: December 16, 2015
Secondary Review Due: December 23, 2015
PDUFA Action Date: March 30, 2016

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

Communication/Document	Date
Information Request 1	May 11, 2015
Information Request 2	July 13, 2015
Information Request 3	August 24, 2015
Information Request 4	September 24, 2015
Information Request 5	October 5, 2015
Information Request 6	October 19, 2015
Information Request 7	October 29, 2015
Information Request 8	November 16, 2015
Information Request 9	November 18, 2015
Information Request 10	November 25, 2015
Information Request 11	December 1, 2015
Information Request 12	December 2, 2015
Information Request 13	December 3, 2015
Information Request 14	December 11, 2015

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed* (Yes/No)
Original submission	March 30, 2015	Yes
Amendment 3	May 22, 2015	Yes
Amendment 9	August 7, 2015	Yes
Amendment 14	September 11, 2015	Yes
Amendment 17	September 30, 2015	Yes
Amendment 20	October 9, 2015	Yes
Amendment 24	October 30, 2015	Yes
Amendment 25	November 5, 2015	Yes
Amendment 26	November 9, 2015	Yes
Amendment 28	November 23, 2015	Yes
Amendment 29	November 24, 2015	Yes
Amendment 30	November 30, 2015	Yes
Amendment 32	December 2, 2015	Yes
Amendment 34	December 4, 2015	Yes
Amendment 35	December 7, 2015	Yes
Amendment 36	December 7, 2015	Yes
Amendment 37	December 7, 2015	Yes

*All or portions of the content of the communications would be directed to the appropriate CMC reviewer (drug product, drug substance, immunogenicity, micro)

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Cinqair
b. Trade Name: Cinqair
c. Non-Proprietary/USAN: reslizumab
d. CAS name: 241473-69-8
e. Common name: CEP-38072
f. INN Name: Reslizumab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMANIZED (IGG4) [redacted] (b) (4) (IL5_HUMAN) [CEP38072]
i. Other Names: CEP-38072, CTx55700, SCH 55700

8. PHARMACOLOGICAL CATEGORY: anti-interleukin 5 monoclonal antibody

9. DOSAGE FORM: Injection

10. STRENGTH/POTENCY: 10 mg/ml

11. ROUTE OF ADMINISTRATION: intravenous infusion

12. REFERENCED MASTER FILES:

DMF #*	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	Sufficient information in the application
			Yes	Sufficient information in the application

*These DMF relate to drug product only

13. INSPECTIONAL ACTIVITIES

It was recommended by the Division of Inspectional Assessment to waive a pre-approval inspection of the drug product manufacturing facility (b) (4) based on the facility's history of compliance with sterile drug product manufacturing and a recent satisfactory inspection (b) (4) that resulted in no FDA Form 483 and was classified as NAI.

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
Maria-Teresa Gutierrez-Lugo PhD Application Technical Lead, Division of Biotechnology Research and Review III	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S Date: 2015.12.16 16:46:38 -05'00'
Tracy A. Denison, PhD Primary Reviewer Division of Biotechnology Research and Review III	Tracy A. Denison -S Digitally signed by Tracy A. Denison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001154781, cn=Tracy A. Denison -S Date: 2015.12.16 16:37:00 -05'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation: **Approval**

With respect to the quality of the drug product, I recommend approval of the BLA. Regarding the adequacy of other components of chemistry, manufacturing, and controls within the BLA refer to the other respective primary reviews.

II. List Of Deficiencies To Be Communicated: **None**

III. List Of Post-Marketing Commitments/Requirement

If the BLA is approved, two Post-Marketing Commitments (PMCs) should be agreed upon. The following is draft PMC language:

1. To reduce the vial overfill to comply with compendial recommendations
2. To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab.

The final study report(s) for the two PMCs will be reported according to 21 CFR 601.12

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review
Refer to review by Dr. Jibril Abdus-Samad

VI. Review Of Common Technical Document-Quality Module 3.2
Find below review of 3.2.P. Refer to Dr. Ramesh Potla's review for review of Section 3.2.S.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4
Refer to review by Dr. Joao Pedras-Vasconcelos

TABLE OF CONTENTS

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

Reslizumab is a humanized anti-interleukin-5 IgG4 antibody. The proposed indication is for use by adolescents and adults with asthma and elevated blood eosinophil levels who are not well-controlled by inhaled corticosteroids. For this subset of asthma patients it is intended to reduce exacerbations, relieve symptoms, and improve lung function. It is produced by recombinant DNA technology expressed in murine NS0 cells. The expected mechanism of action is to bind to interleukin-5 (IL-5) and prevent it from binding to the IL-5 receptor. The drug product presentation of reslizumab is a colorless to slightly yellow aqueous solution supplied in 10 ml and containing 100 mg of reslizumab, which is a concentration of 10 mg/ml. It is provided sterile and without preservatives, and is diluted with saline prior to infusion. It is provided in a Type I clear, borosilicate glass vial. The closure includes a (b) (4) rubber stopper which is sealed over with an aluminum flip-off seal. Each vial is intended for single use only and remaining drug product must be discarded after use. Patients are to be dosed at 3 mg/kg every four weeks.

3.2.P.2 Pharmaceutical Development

The following section reviews aspects of the pharmaceutical development of the reslizumab drug product.

3.2.P.2.1 Components of the Drug Product

The following table lists the components in the reslizumab drug product.

Table 1: Composition of the Reslizumab Drug Product

Component	Amount per mL	Reference to Standard	Function
Reslizumab (CEP-38072) protein	10 mg	In house specifications	Drug substance
Sucrose (b) (4)	70 mg	NF/Ph. Eur./JP	(b) (4)
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	
(b) (4)			

3.2.P.2.1.1 Drug Substance

(b) (4)

Drug product reslizumab concentration is 10 mg/ml.

3.2.P.2.1.2 Excipients

The excipients for reslizumab include the following components listed in the following table, with respective information for grade and formulation function.

Table 1: (b) (4)

Component	Amount per mL	Reference to Standard	Function
Sucrose (b) (4)	70 mg	NF/Ph. Eur./JP	(b) (4)
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	
			(D) (4)

Reviewer's Comment: The components of the drug product formulation are appropriate. The active ingredient will be controlled as reviewed later and other components of the formulation are held to compendial standards generally recognized in the United States. Every component has a defined purpose.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(b) (4) The proposed commercial manufacturing of drug product will be identical to that used in the Phase 3 clinical trial.

3.2.P.2.2.2 Overages

There are (b) (4) of product in the drug product formulation.

3.2.P.2.2.3 Physicochemical and Biological Properties

The reslizumab drug product has (b) (4) 10 mg/ml. The following table provided by the sponsor indicates some properties of reslizumab drug product during development.

52 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

BLA STN 761033

Reslizumab

Teva Pharmaceuticals

Ramesh Potla, PhD
Maria Teresa Gutierrez, PhD
Division of Biotechnology Review and Research III

OBP CMC Review Data Sheet

1. **BLA#:** STN 761033

2. **REVIEW DATE:** December 16, 2015

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Kathleen Donohue
Pharm/Tox: Carol Galvis
Product Quality Team: Ramesh Potla (drug substance), Tracy Denison (drug product)
OBP Immunogenicity: Joao Pedras-Vasconcelos
Product Quality Microbiology (DS): Bo Chi
Product Quality Microbiology (DP): Laskhmi Narasimhan
BMT or Facilities: Thuy Nguyen
Clinical Pharmacology: Yunzao Ren
Statistics: Lan Zeng
OBP Labeling: Jibril Abdus-Samad
OBP RPM: Andrew Shiber
Clinical RPM: Colette Jackson

4. **MAJOR GRMP DEADLINES**
Filing Meeting: May 11, 2015
Mid-Cycle Meeting: August 28, 2015
Wrap-Up Meeting: February 04, 2016
Primary Review Due: December 16, 2015
Secondary Review Due: December 23, 2015
PDUFA Action Date: March 30, 2016

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

Communication/Document	Date
Information Request 1	May 11, 2015
Information Request 2	July 13, 2015
Information Request 3	August 24, 2015
Information Request 4	September 24, 2015
Information Request 5	October 5, 2015
Information Request 6	October 19, 2015
Information Request 7	October 29, 2015
Information Request 8	November 16, 2015
Information Request 9	November 18, 2015
Information Request 10	November 25, 2015
Information Request 11	December 1, 2015
Information Request 12	December 2, 2015
Information Request 13	December 3, 2015
Information Request 14	December 11, 2015

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

Submission	Date Received	Review Completed* (Yes/No)
Original submission	March 30, 2015	Yes
Amendment 3	May 22, 2015	Yes
Amendment 9	August 7, 2015	Yes
Amendment 14	September 11, 2015	Yes
Amendment 17	September 30, 2015	Yes
Amendment 20	October 9, 2015	Yes
Amendment 24	October 30, 2015	Yes
Amendment 25	November 5, 2015	Yes
Amendment 26	November 9, 2015	Yes
Amendment 28	November 23, 2015	Yes
Amendment 29	November 24, 2015	Yes
Amendment 30	November 30, 2015	Yes
Amendment 32	December 2, 2015	Yes
Amendment 34	December 4, 2015	Yes
Amendment 35	December 7, 2015	Yes
Amendment 36	December 7, 2015	Yes
Amendment 37	December 7, 2015	Yes

*All or portions of the content of the communications would be directed to the appropriate CMC reviewer (drug product, drug substance, immunogenicity, micro)

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Cinqair
   b. Trade Name: Cinqair
   c. Non-Proprietary/USAN: reslizumab
   d. CAS name: 241473-69-8
   e. Common name: CEP-38072
   f. INN Name: Reslizumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMANIZED (IGG4) (b) (4) (IL5_HUMAN) [CEP38072]
   i. Other Names: CEP-38072, CTx55700, SCH 55700

8. **PHARMACOLOGICAL CATEGORY:** anti-interleukin 5 monoclonal antibody
9. **DOSAGE FORM:** Injection
10. **STRENGTH/POTENCY:** 10 mg/mL
11. **ROUTE OF ADMINISTRATION:** intravenous infusion
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted] (b) (4)			Yes	I reviewed the Master File and found it acceptable to support BLA 761033

*This Biologics Master File relates to drug substance only

13. **INSPECTIONAL ACTIVITIES**

This pre-license inspection of the drug substance manufacturing facility [redacted] (b) (4) was conducted [redacted] (b) (4) following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, under FACTS assignment # [redacted] (b) (4) The inspection covered drug substance manufacturing areas [redacted] (b) (4) and warehouse [redacted] (b) (4) and an offsite warehouse [redacted] (b) (4) The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products; CP 7346.832, Pre-Approval Inspections/Investigations; and ICH Q7. This inspection was limited to the manufacturing of reslizumab [redacted] (b) (4)

A seven-item 483 was issued. See Appendix 1 for a copy of FDA-483. The recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived.

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
Maria-Teresa Gutierrez-Lugo, Ph.D. Application Technical Lead Division of Biotechnology Research and Review III Office of Biotechnology Products	Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=001181 8863, cn=Maria Teresa Gutierrez Lugo -S Date: 2015.12.16 22:03:44 -05'00'
Ramesh Potla, Ph.D. Primary Reviewer Division of Biotechnology Research and Review III Office of Biotechnology Products	Ramesh B. Potla -S Digitally signed by Ramesh B. Potla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012 101865, cn=Ramesh B. Potla -S Date: 2015.12.16 21:45:45 -05'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of STN 761033 for Cinqair (reslizumab). The data submitted in the Biologics License Application support the conclusion that the manufacture of Cinqair (reslizumab) is well controlled and leads to a product that is pure and potent. The reslizumab drug substance is free from endogenous and adventitious agents sufficient to meet the parameters recommended by the FDA. The conditions used for manufacturing reslizumab drug substance have been sufficiently validated, and consistent product has been manufactured from the multiple production runs. The Office of Biotechnology Products recommends Cinqair (reslizumab) be approved for human use (under conditions specified in the package insert).

The Office of Biotechnology Products recommends an expiry period of 36 months for reslizumab drug substance when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirement

If the BLA is approved, two Post-Marketing Commitments (PMCs) should be agreed upon. The following is draft PMC language:

1. To improve the overall control strategy of the drug substance manufacturing process (b) (4)
2. To implement (b) (4) in the drug substance manufacturing process.

The final study report(s) for the two PMCs will be reported according to 21 CFR 601.12

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

Refer to Review by Dr. Jibril Abdus-Samad

VI. Review Of Common Technical Document-Quality Module 3.2

Find below review of 3.2.S. Refer to Dr. Tracy Denison's review for Section 3.2.P.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Refer to review by Dr. Joao Pedras-Vasconcelos

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

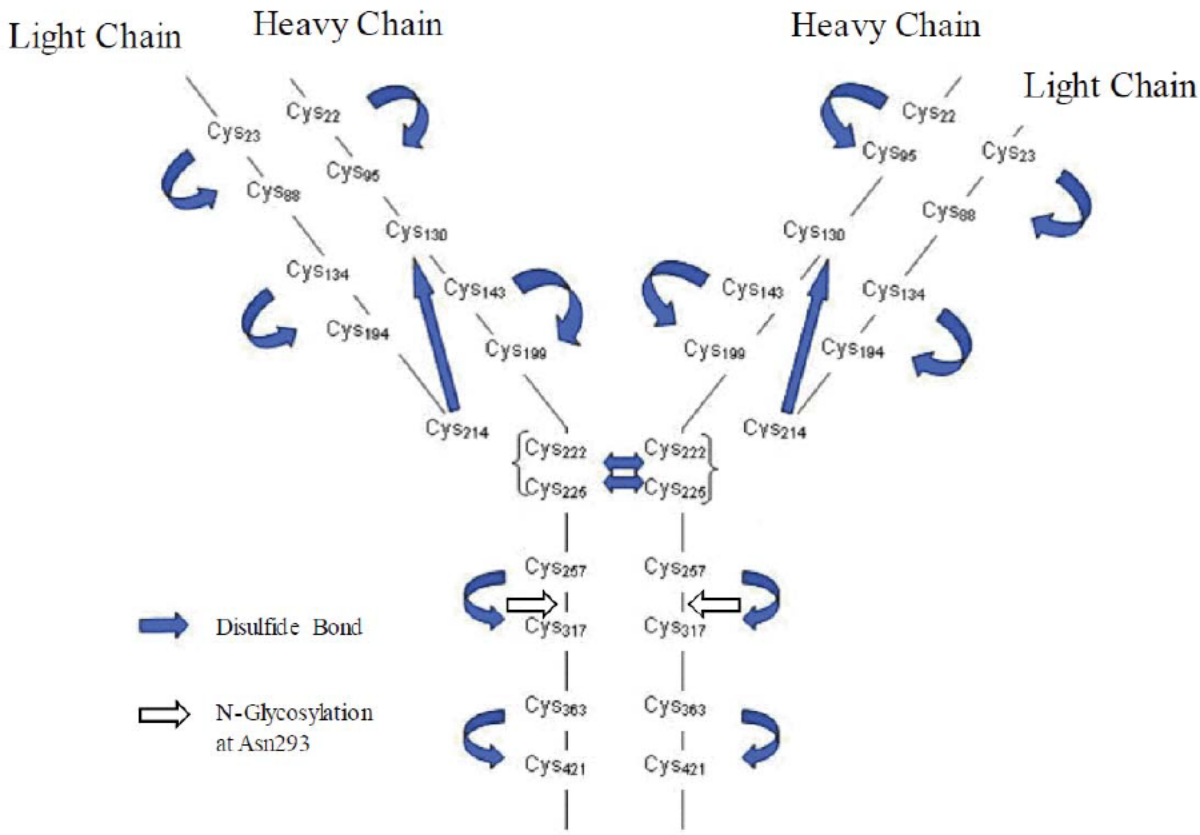
Unless explicitly indicated, all figures and tables in this review are copied directly from the BLA submission or from information request responses.

S. DRUG SUBSTANCE

3.2.S.1.2 Structure

Reslizumab (CEP-38072) is a recombinant, humanized IgG_4, κ monoclonal antibody to the human interleukin-5 (anti-IL-5 MAb). Reslizumab contains the complementary determining regions (CDRs) of the original rat antihuman antibody 39D10 grafted onto a human framework. It is composed of two light chains and two heavy chains linked by 12 intra-chain and 4 inter-chain disulfide bonds. (b) (4) N-linked (b) (4) oligosaccharides of reslizumab are derived from NS0 cell lines. The predicted molecular mass is 146.8 kDa. The schematic diagram of reslizumab is shown below:

Figure 1: Structural Representation of Reslizumab Disulfide Bond Linkage



The predicted amino acid sequence of reslizumab is provided below:

Table 1: Theoretical Amino Acid Sequence for Reslizumab

(b) (4)

Light Chain

(b) (4)

Reviewer Comment: (b) (4)

3.2.S.1.3 General Properties

Reslizumab is a humanized IgG_4, κ monoclonal antibody produced in a NS0 cell line. Reslizumab binds to soluble circulating human IL-5 and prevents its binding to the IL-5 receptor on eosinophils, thereby inhibiting their proliferation and activation. The drug substance (DS) contains reslizumab at (b) (4) mg/mL concentration (b) (4) The properties of reslizumab are provided in the table below:

Table 1: Reslizumab Drug Substance General Properties

Property	Description
Appearance Clarity and degree of opalescence of a liquid	Clear to slightly hazy/opalescent solution
Appearance Degree of coloration	Colorless to slightly yellow/yellow solution
Protein type	Human IgG4, kappa
Amino acid sequence	Section 3.2.S.1.2, Table 1
Molecular mass (theoretical)	146,776 Da (b) (4)
Glycosylation	N-Glycosylated at Asn293 (b) (4)
UV Extinction coefficient at the wavelength of A (b) (4)	(b) (4)
pH at (b) (4) °C	
Protein concentration	
pI of main peak	
Osmolality	
Thermodynamics	
Sedimentation coefficient	
Disulfide linkage	16 disulfide bonds
Biological activity	Inhibition of proliferation of (b) (4) cells Potency: (b) (4) % relative potency

Reviewer Comment: (b) (4) *The recommended storage conditions for both DS and DP are 5±3 °C.*

Reslizumab's Mechanism of Action:

Reslizumab is a humanized IgG4 monoclonal antibody that binds to and neutralizes human IL-5. IL-5 mediates the proliferation, activation, and survival of target eosinophil cells. The mechanism of action for reslizumab is achieved by blocking IL-5 binding capacity to its specific receptor. Using a combination of synthetic peptide mapping and site-directed mutagenesis studies, it is determined that reslizumab recognizes a tetrapeptide with amino acid residues 89 – 92 (E89, R90, R91, and R92) as the minimal epitope on human IL-5. In addition, results from amino acid substitution studies showed that an additional three amino acid residues (K85, G87, and N94)

located in the vicinity of the minimal epitope region also impact the binding of reslizumab to IL-5 (Zhang et al, 1999). Three (E89, R90, and R91) out of 4 amino acid residues located in the minimal epitope region of human IL-5 are also confirmed as key residues for the interaction of IL-5 with human IL-5 receptor α complex (Graber, 1995; Tavernier, 1995; and Patino et al, 2011). Overall, the provided information demonstrate that reslizumab neutralizes soluble IL-5 and prevents this cytokine from binding to IL-5 receptor α, thereby preventing the activation of eosinophils and their consequent mobilization into the bronchial airspace. See Figures 1 and 2 below for schematic diagram(s) on reslizumab's mechanism of action.

Figure 1: Reslizumab Mechanism of Action

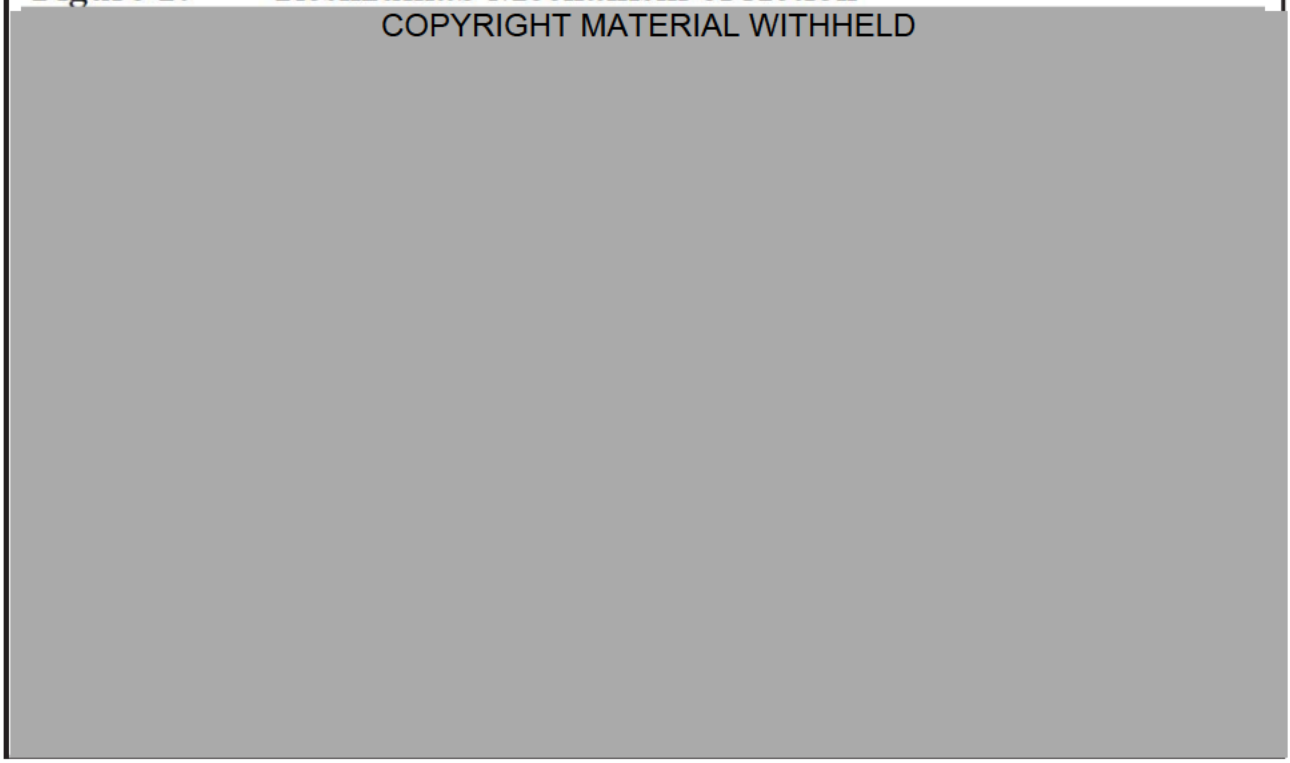
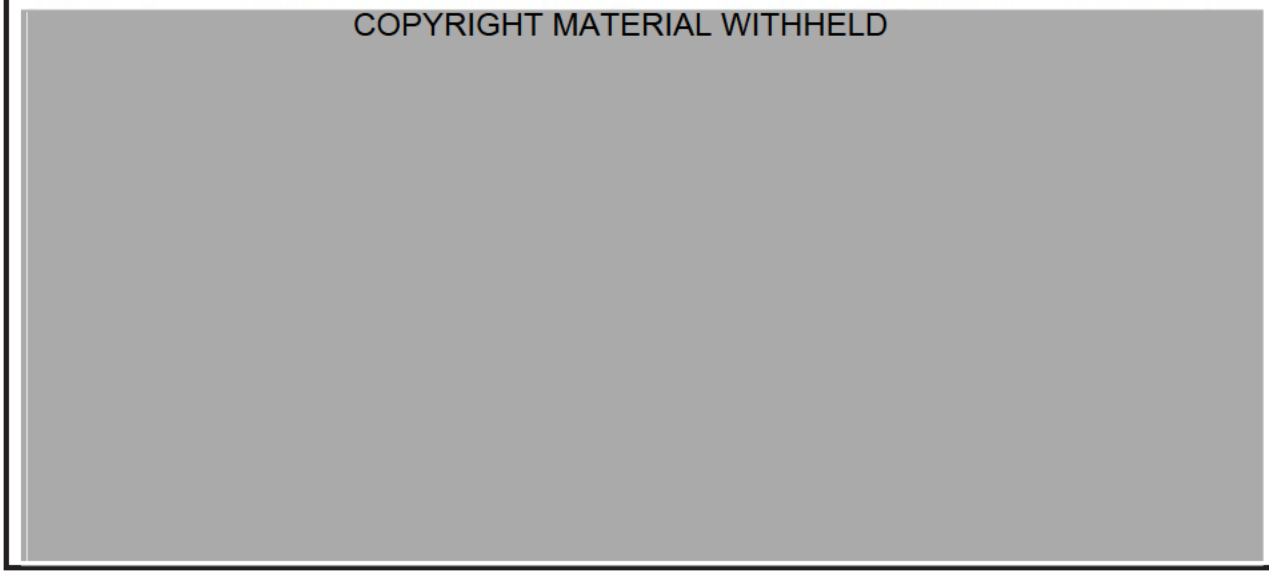


Figure 2: Human IL-5 Interacting with IL-5 Receptor α at Residues E^{89}, R^{90}, and R^{91}



3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Reslizumab DS is manufactured [redacted] (b) (4) for Teva Pharmaceuticals. The manufacturing, testing and storage sites for reslizumab DS are shown in the table below:

222 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: 12/15/2015

From: Thuy T. Nguyen, MPH, OPQ/OPF/DIA
Tracy Denison, Ph.D., OPQ/OBP
Lakshmi Narasimhan, Ph.D., OPQ/OPF/DMA

To: BLA File, STN 761033/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of reslizumab drug product at [redacted]

Applicant: Teva Branded Pharmaceutical Products R&D, Inc.

Facility: [redacted]
FEI: [redacted]

Product: Reslizumab Solution for Infusion

Dosage: 3mg/kg Intravenous Use.

Indication: To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

Waiver Recommendation

Reslizumab Drug Product (DP) is manufactured, inspected, packaged and labeled [redacted] The proposed commercial product manufacturing operations for reslizumab DP includes [redacted] filling and capping; and final 100% inspection and packaging.

The drug product is manufactured at 10 mg/mL strength (10mL single-use vials) and a batch size [redacted]

The proposed commercial manufacturing scheme for reslizumab is [redacted] manufactured [redacted]

The facility was inspected [redacted] covered SVS profile. The inspection resulted in no FDA Form 483 and was classified NAI. There were no concerns related to manufacture of sterile product [redacted] at the facility. Based on the firm's compliance history and current acceptable GMP status, we recommend that inspection of [redacted] facility be waived for BLA 761033/0.

Summary

BLA 761033/0 was submitted by Teva Branded Pharmaceutical Products R&D, Inc. and it provided information and data to support the manufacture of reslizumab, Injection, 100mg/10mL vial. The manufacture of Reslizumab drug substance is performed [redacted] and reslizumab drug product is manufactured [redacted] The current waiver recommendation is in regards to drug product manufacture [redacted]

Facility Information

[redacted] facilities are multi-product facilities and are used for the manufacture of drug products and biologics. Change over procedures are implemented [redacted] Pharmaceutical preparations are performed [redacted]

The reslizumab Bulk Drug Substance (BDS) is received [redacted] The amount of BDS required for each batch is calculated based on [redacted].

[redacted]

The manufacture of reslizumab DP employs [redacted] filling and capping; and final 100% inspection and packaging.

The drug product is manufactured at 10 mg/mL strength and a batch size of [redacted]L [redacted]

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   The (b) (4) site is a multi-product facility manufacturer. This facility has already been approved for commercial manufacture (b) (4)

2. *The previous inspection revealed significant GMP deficiencies* (b) (4)

   The facility was inspected (b) (4) covered SVS profile. The inspection resulted in no FDA Form 483 and was classified NAI. There were no concerns related to manufacture of sterile product (b) (4) at this facility.

3. (b) (4)

   The manufacturing areas, (b) (4) are currently approved (b) (4) This area has been qualified for sterile products.

4. *The manufacturing process is* (b) (4) *produced by the establishment.*

   The proposed manufacturing operations for reslizumab Injection are (b) (4)

Signed:

Thuy T. Nguyen, MPH, OPF/DIA Reviewer _____

Tracy Denison, Ph.D., OPQ/OBP Reviewer _____

Lakshmi Narasimhan, Ph.D.,OPF/DMA Reviewer_____

Maria-Teresa Gutierrez-Lugo, Ph.D., OPQ/OBP ATL_____

Patricia Hughes, Ph.D., OPF/DMA Acting Branch Chief _____

Zhihao Qiu, Ph.D., OPF/DIA Branch Chief _____

Amy Rosenberg, MD., OPQ/OBP _____

My Work Projects Reporting Requests Timesheet

Search All...

Because you're using an older browser, your Workfront experience isn't all that it should be. We seriously recommend exploring other options.

BLA 761033-Orig1-New - Proprietary Name - User Fee - Form 3674/BLA ... » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Issues | Updates | Inspection Management Form

Inspection Management Form As of 6:26 PM

Inspection Management Form

BLA 761033-Orig1-New - Proprietary Name - User Fee - Form 3674/BLA - Request for Review - Coversheet (1)

(b) (4)

Overall Manufacturing Inspection Recommendation

- (•) Approve
- ( ) Withhold

Save Cancel

Assigned To

Thuy Nguyen

IM - OPF Reviewer

Edit Assignment

This was done on
Dec 7, 2015
(73 days ago)

Status
Complete

Requested by

DARRTS Integration

This task is waiting on
2 Tasks

Last Update
Feb 16, 2016

Submitted On
Mar 31, 2015

Reference Number
4224496

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: 11/11/2015
To: Administrative File, STN 761033
From: Thuy T. Nguyen, Facility Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 2016
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.
Mfg Facility: Drug Substance: (b) (4)
FEI (b) (4)
Drug Product: (b) (4)
FEI (b) (4)
Product: Reslizumab Injection
Dosage: 3mg/kg Intravenous Use
Indication: To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Due Date: 12/16/2015

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

SUMMARY

The subject BLA proposes manufacture of Reslizumab Drug Substance (b) (4) , and Drug Product (b) (4) Cell banking operations will occur (b) (4) Testing operations will occur at (b) (4) Teva Pharmaceutical Works Private Limited, Debrecen, Hungary (FEI 3006067169), (b) (4)

Reslizumab is a humanized anti-interleukin-5-monoclonal antibody (anti-IL-5 mAb) of the immunoglobulin-G4 kappa (IgG4/k) isotype and is presented as a 100 mg in a single-use 10 mL

vial. Reslizumab is intended to be administered as an intravenous (IV) infusion at a dose of 3 mg/kg every 4 weeks to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Reslizumab DS manufacture, cell banking operations, and testing are presented below in Table 1. .

Table 1: Proposed Sites for Reslizumab DS Manufacture, Cell Banking and Testing Operations

Name and Address of Site	Activities Performed	FEI Number
(b) (4)		FEI: (b) (4)
		FEI: (b) (4)
		FEI: (b) (4)
Teva Pharmaceutical Works Private Limited Company Site 1, Pallagi St. 13 Debrecen, 4042, Hungary	Release and stability testing: (b) (4) Inhibition Bioassay	FEI: 3002806524

18 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

**This able is a copy of Table 4 in Module 3.2.A.3.6.*

***Reviewer Comment 17**: The major equipment used for reslizumab DP manufacture (b) (4) was adequately described.*

- **3.2.A.1.3.8. Equipment Qualification**
  Equipment qualification consists of equipment validation, cleaning validation and sterilization validation; it is performed upon new equipment introduction or changes to existing equipment. Qualification/validation requirements are based upon the equipment's intended use and the potential to adversely affect product quality.

  Cleaning validation is performed for all surfaces with direct product contact and some with indirect product contact, dependent on the risk to the product. The substances/products in contact with the equipment are evaluated using worst-case. Sampling points are selected according to equipment design, accessibility and the cleaning process. Test parameters are defined to include (b) (4) substances as well as microbial contaminations.

  Sterilization processes are validated with three validation runs under worse-case conditions. Sterilization processes are revalidated annually.

  ***Reviewer Comment 18**: The equipment qualification for equipment used in the manufacture of reslizumab DP (b) (4) was adequately described.*

CONCLUSION

Adequate descriptions were provided for the (b) (4) facilities proposed for Reslizumab DS and DP manufacture. All proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Thuy T. Nguyen -S

Digitally signed by Thuy T. Nguyen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thuy T. Nguyen -S, 0.9.2342.19200300.100.1.1=2000425639
Date: 2015.12.14 08:53:26 -05'00'

Thuy T. Nguyen, M.P.H.
Facility Reviewer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274
Date: 2015.12.14 09:08:19 -05'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1