

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761033Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



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

Date: December 15, 2015
To: Administrative File, BLA 761033/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 2016
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.
Facility: [REDACTED] (b) (4)
Product: Reslizumab (Cinqair)
Dosage: Sterile, liquid formulation (10mg/mL) in a single use vial for intravenous injection
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 (Proposed)
Due Date: March 28, 2016

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):

- 1. 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 \leq (b) (4) μ m and submit the data by April 2016.*
- 2. The performed microbial retention study 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 [REDACTED] (b) (4) and drug product is manufactured [REDACTED] (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	(b) (4)
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 25°C (77°F), 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 25°C. 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 *Propionibacterium acnes* (ATCC 6919). The bags were stored at 2-8°C and room temperature (20-25°C) and sampled at 0,



- 3. Teva commits to repeat the dye ingress CCI study using reslizumab 10 mL/20 mm vial with controls containing (b) (4) breach sizes (\leq (b) (4) μ) (b) (4). The results of this study will be submitted no later than 6 months from the response date of October 30, 2015.

PMC 1: *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 \leq (b) (4) μ and submit the data by April 2016.*

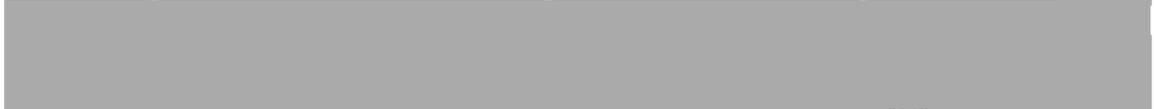
Pending PMC Satisfactory

Capping Force:

FDA question (August 23, 2015):

- 1. *Please provide CCI test results obtained using with worst-case crimping process parameters to qualify the container closure system for reslizumab drug product*

Firm's Response in amendment dated September 11, 2015 in sequence # 0013: (b) (4)



Test vials were generated (b) (4) are subjected to CCI testing (Report, VL1104018) and all test vials met the acceptance criteria.

Satisfactory

3.2.P.3.1. MANUFACTURER(S)

The following table listing the manufacturing and testing sites conducting release and stability tests for DP is formulated from the information provided in the application.

Name and address of manufacturer	Activities Performed	Status (FEI) Number (DUNS) Number
(b) (4)		GMP FEI: (b) (4) DUNS: (b) (4)

(b) (4)		
		GMP FEI: (b) (4) DUNS : (b) (4)
		GMP FEI: (b) (4) DUNS : (b) (4)
Teva Pharmaceutical Works, plc. Pallagi Street 13 H-4042 Debrecen Hungary	Release & stability testing of finished product: (Potency Bioassay)	GMP FEI: 3006067169 DUNS: 463612064

Reviewer’s comments: Pre-license inspection of (b) (4) facility was waived. See Panorama.

3.2.P.3.2. BATCH FORMULA

DP batch sizes ranging from (b) (4) L to (b) (4) L were manufactured during process validation. (b) (4)

The batch formula to process a representative (b) (4) L batch size provided in Table 1 of the submission is reproduced below.

Table 1: Representative (b) (4) L Batch Formula for Reslizumab Solution for Infusion Drug Product (10 mg/mL)

Ingredient	Quantity per mL	Quantity per batch (b) (4) L
Reslizumab protein	10.0 mg	(b) (4)
Sucrose (b) (4) (NF/Ph. Eur./JP)	70 mg	(b) (4)
Sodium Acetate Trihydrate (USP/Ph. Eur./JP)	2.45 mg	(b) (4)
Glacial Acetic Acid (USP/Ph. Eur./JP)	0.12 mg	(b) (4)

Satisfactory

3.2.P.3.3. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

The drug product is manufactured at 10 mg/mL strength and a batch size of (b) (4) L (b) (4). The following DP manufacturing process flow diagrams are reproduced from the submission.

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

Firm's Response in amendment dated November 25, 2015 in sequence # 0029: (b) (4) bioburden ((b) (4) CFU/100 mL) and endotoxin ((b) (4) EU/mL) limits were included into the manufacturing batch record (effective 16 October 2015).

Reviewer's comments: Drug product manufacturing process is adequately described.

Satisfactory

3.2.P.3.4 Controls of Critical Steps and Intermediates

The in-process controls (b) (4) are shown in the table 3 below, which were provided in submission.

Table 3: In-Process Control Tests for Reslizumab (b) (4)

Process Step	In-Process Control Test	Test Method	Acceptance Criteria
(b) (4)			

Satisfactory

3.2.P.3.5. PROCESS VALIDATION AND/OR EVALUATION

Process Validation

(b) (4)

3.2.P.4 CONTROL OF EXCIPIENTS:

This section should be reviewed by OBP

3.2.P.5 CONTROL OF DRUG PRODUCT**3.2.P.5.1. Specifications**

The microbial for the drug product release specifications are reslizumab should be sterile with endotoxin limit of \leq (b) (4) EU/mg.

Reviewer's comments: The set endotoxin limit has not considered any safety factor. In response to Agency's IR, Teva tightened the DP endotoxin limit to (b) (4) EU/mg which provides (b) (4) fold safety factor.

Satisfactory

3.2.P.5.2. Analytical procedures

Endotoxin: The presence of endotoxin in drug product samples is determined using kinetic chromogenic LAL method in compliance with USP <85>, and Ph. Eur 2.6.14.

Sterility: Sterility testing of drug product for release is performed (b) (4) according to the USP<71>, JP 4.05 and Ph. Eur 2.6.1.

Bioburden: (b) (4) bioburden testing of bulk drug product is performed (b) (4) in compliance with USP <61>, and Ph. Eur 2.6.12.

3.2.P.5.3. Validation of Analytical procedures

Endotoxin Method Qualification: BER10-10-001, Method Development Report is provided. (b) (4)

(b) (4) Table 1 and 2 of this report indicate that standard curve parameters and coefficient of variation for standards were met. Table 3 showing the (b) (4) results from Batch 915657 is reproduced below.

Table 3
Batch 915657 (b) (4) **Results** (b) (4)



Based on these results (b) (4) were tested (b) (4) from batch 915657. The use (b) (4) was confirmed (b) (4) from batch, 915657. These tests were performed (b) (4). Table 4, 5, 7 and 8 of this report indicate that standard curve parameters and coefficient of variation for standards were met. Table 6 and 9 (b) (4) from Batch 915657 is reproduced below.

Table 6
Batch 915657 (b) (4) **Results** (b) (4)



Table 9
915657 (b) (4) **Results** (b) (4)



Additional three lots, 917774, 918503 and 918504 were used to validate this endotoxin assay. Result tables, 9, 15 and 18 indicated that all acceptance criteria were met.

FDA question (October 19, 2015): Please provide the rationale (b) (4) in the endotoxin assay method validation.

Firm's response in May 21, 2015 amendment (Sequence 0024): (b) (4)

(b) (4) is used in the endotoxin assay method validation.

Satisfactory

Rabbit pyrogen test:

FDA question (May 11, 2015): Please provide information and summary data for the rabbit pyrogen test of reslizumab in conformance to 21CFR 610.13 (b). The rabbit pyrogen test should be done at least once with 3 lots of finished drug products to demonstrate that the product does not contain pyrogenic substances other than bacterial endotoxin.

Firm’s response in May 21, 2015 amendment (Sequence 0003): Rabbit Pyrogen testing was performed for three drug product lots in compliance with USP <151>. The results are summarized in Table 7 of Section 3.2.P.5.4, reproduced below; indicate DP samples were negative for pyrogens.

Table 7: Results from Rabbit Pyrogen Test

DP Lot Number	Acceptance Criterion	Result
11-002804	Negative for the presence of pyrogens	Pass
12-000792	Negative for the presence of pyrogens	Pass
12358	Negative for the presence of pyrogens	Pass

FDA question (August 23, 2015): Please submit the report providing the information and result summary data of rabbit pyrogen testing performed with 3 lots of finished drug products of reslizumab

Firm’s response in September 11, 2015 amendment (Sequence 013): Report, TR-Q-43, “Determination of Pyrogenicity in Reslizumab, DP” which included the results of the pyrogen test performed with lots of DP (11-002804, 12-000792, and 12358) was provided. (b) (4)

(b) (4)
The test met the requirements of the pyrogen test (b) (4)

FDA question (October 19, 2015): Please clarify if the Rabbit pyrogen test studies were performed with commercial manufacturing DP lots.

Firm’s Response in amendment dated October 30, 2015 in sequence # 0024: Teva confirmed that the DP batches (11-002804, 12-000792, and 12358) used for the rabbit pyrogen study are representative of the commercial manufacturing process.

Satisfactory

Low endotoxin Recovery

FDA question (May 11, 2015): Please provide evidence that the drug product formulation does not interfere with endotoxin recovery in the LAL test. Conduct spiking studies on the undiluted drug product with known amount of endotoxin and simulate the

worst-case hold conditions to evaluate endotoxin masking over time. The studies should be conducted using containers of similar composition as those used for the drug product.

Firm's response in May 21, 2015 amendment (Sequence 0003): Endotoxin recovery was assessed by spiking endotoxin into undiluted samples. Report TR-Q-33, Endotoxin spiking study in CEP-38072 drug substance and drug product and BDS included in Section 3.2.S.4.3. (b) (4)

The endotoxin result from the spiked samples at each time point was compared to T₀ control for % recovery assessment and summarized in the Table 6 reproduced below.

Table 6: Endotoxin % recovery values for Drug Product

Drug Product
(b) (4)

Drug Product showed satisfactory endotoxin recovery (b) (4)

Satisfactory

Sterility test Method Qualification:

Two reports, 07-02-F002-24.0 and 07-02-F002-25, "Determining Bacteriostasis/Fungistasis Activity of Bulk and Finished Products" were provided. Report 07-02-F002-24.0 states (b) (4) used in the method verification study. It is not clear if the method verification results provided are from the DP (b) (4) Report 07-02-F002-25 provides the method verification results from DP batch number 916273. (b) (4)

(b) (4)

FDA question (October 19, 2015):

1. *It is not clear whether the sterility test method qualification was performed with drug product manufactured by the commercial process* (b) (4)
Please respond to the following comments.
 - a. *Section 3.2.P.5.3 states that the sterility test method validation was conducted on two reslizumab drug product batches (10-001036 and 10-000862) while the Report 07-02-F002-24.0 “Determining Bacteriostasis/Fungistasis Activity of Bulk and Finished Products” states* (b) (4)
 used in the method verification study and Report 07-02-F002-25 provides the sterility method verification results from DP batch number 916273. Please clarify the discrepancy.
 - b. *Please clarify if the sterility test method qualification studies were performed with commercial manufacturing DP lots.*
 - c. *Please clarify if the method verification results provided in Report 07-02-F002-24.0 are from the DP* (b) (4)
2. *Please provide details of the sterility test method qualification* (b) (4)

Firm’s response in October 30, 2015 amendment (Sequence 0024):

1. Sterility test method qualification was performed with two reslizumab drug product (active) batches ((b) (4) lots 915657 and 916273) which are representative of the commercial formulation as per 07-02-F002-24.0 and 07-02-F002-25.0. (b) (4)
Six-digit lot numbers starting with “9” represents (b) (4) lot number, lot number, 10-001036 represent Teva’s lot number. (b) (4) documents reference the (b) (4) lot number. Table 2 in Section 3.2.P.2.3 was referenced for DP lot number cross-reference listing: (b) (4) lots 915657 and 916273 are referred as Teva lots 10-001036 and 10-000862.
2. (b) (4)

FDA question (November 18, 2015): Sterility method qualification has been completed using only two drug product lots. Please submit the sterility test method qualification information and results from study performed using an additional commercial drug product lot.

Firm’s Response in amendment dated November 24, 2015 in sequence # 0029: Document 07-02-F002-27 providing the sterility method qualification results for DP lot # 928052 manufactured using the commercial formulation and commercial process is included with the response. In the presence of DP, no inhibitory effect was noted with any of the

challenge microorganisms. Challenge organism inoculum was < (b) (4) CFU. Gram staining of the organisms from test and positive control container confirmed the challenge organisms.

Reviewer's comments: (b) (4) sterility testing indicated that the DP was not inhibitory to the tested challenge organisms.

Satisfactory

Bioburden test:

FDA question (May 11, 2015): Provide the details of bioburden testing and method qualification summary data from 3 formulated bulk drug product lots.

Firm's response in May 22, 2015 amendment (Sequence 0003):

As per Report (b) (4)-103, Method validation-bioburden (b) (4) of bioburden testing is used for bulk drug product lots. The method verification was conducted on three reslizumab drug product batches. (b) (4)

The challenge results are presented in Table 5.

Table 5: Challenge Organisms

Organism Name	ATCC Number	% Recovery		
		11-000701	11-002802	11-002803
(b) (4)				

The method verification data indicates that the drug product did not inhibit the growth of any of the challenged microorganisms with > (b) (4) % recovery and is suitable for testing bioburden in drug product samples.

FDA Question: (October 19, 2015): Please clarify the discrepancy, Report (b) (4)-103, Method validation-bioburden, provides the bioburden method validation results from batch numbers 917774, 918503, and 918504 while Section 3.2.P.5.3 provides the method validation results of batches 11-00001, 11-002802 and 11-002803.

Firm's response in October 30, 2015 amendment (Sequence 0024): (b) (4) batch numbers 917774, 918503, and 918504 correspond to DP batches assigned by Teva, 11-000701, 11-002802, and 11-002803 respectively.

Satisfactory

3.2.P.5.4 Batch Analyses

All drug product lots manufactured met the endotoxin (< (b) (4) EU/mL) and sterility acceptance criteria.

Reviewer's comments: Results other than sterility and endotoxin should be reviewed by OBP reviewer.

Satisfactory

3.2.P.5.6 Justification of Specification

Endotoxin

The endotoxin specification is \leq (b) (4) EU/mg. For reslizumab DP the maximum human dose is 3.0 mg/kg of body mass in a single hour period. Based on the endotoxin limit calculation, K/M, the endotoxin limit for reslizumab is (b) (4) EU/mg (K/M = (b) (4)).

FDA question (August 23, 2015): The proposed commercial specification endotoxin limit \leq (b) (4) EU/mg does not provide any safety factor. Additionally, the DP is diluted in 0.9% sodium chloride injection USP prior to administration by intravenous infusion. Endotoxin levels at release and during stability at 2 to 8°C < (b) (4) EU/mg. Please tighten reslizumab DP release endotoxin specification to provide a safety margin.

Firm's response in September 11, 2015 amendment (Sequence 013): Teva agreed that DP endotoxin limit should be tightened to provide a safety margin. USP's recommendation for DP endotoxin limit, DS endotoxin specification, historical endotoxin data of the DP batches and the endotoxin from the 0.9% sodium chloride are considered and a new endotoxin specification of (b) (4) EU/mg that provides (b) (4) safety margin is proposed for the DP.

Reviewer's comments: Tightening of endotoxin limit from \leq (b) (4) EU/mg to (b) (4) EU/mg provides (b) (4) fold safety factor.

FDA question (October 29, 2015): Please update sections 3.2.P.5.1 and 3.2.P.5.6 of the BLA application with the tightened endotoxin specification of (b) (4) EU/mg.

Firm's response in November 09, 2015 amendment (Sequence 026): Table 1 of Section 3.2.P.5.1 has been updated with the tightened endotoxin specification of \leq (b) (4) EU/mg protein. Section 3.2.P.5.6.4.13 has been updated with the justification for the tightened endotoxin specification.

Satisfactory

3.2.P.7 CONTAINER CLOSURE SYSTEM

The commercial container closure system for DP consists of 10 mL Type I, clear, borosilicate glass tubing vial, 20 mm (b) (4) rubber stopper, and a 20 mm aluminum crimp seal having a royal blue plastic flip-off cap. Vials and stoppers are purchased (b) (4)

(b) (4) Each lot of vial and stopper lot is accepted by the Certificate of Analysis from the qualified supplier. Additionally, (b) (4) performs a complete testing of vials and stoppers (b) (4)

(b) (4) Stoppers should meet the requirements for the absence of pyrogens. Specifications and drawings of the container closure components are presented.

Satisfactory

3.2.P.8 STABILITY

DP lots were evaluated at the following conditions, recommended, 2-8°C, accelerated, 25°C/60%RH and stressed, 40°C/75%RH. Based on these data, a 36-month shelf life is proposed for DP.

POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

[Redacted]

FDA question (August 23, 2015): We recommend [Redacted]

Firm's response in September 11, 2015 amendment (Sequence 013): The sponsor has agreed to perform [Redacted]

FDA question (November 24, 2015): Please update sections 3.2.P.5.1 and 3.2.P.8.2 of the BLA application [Redacted] *as described in your communication dated September 11, 2015.*

Firm's response in December 02, 2015 amendment (Sequence 032): Sections 3.2.P.5.1 and 3.2.P.8.2 of the BLA have been updated to [Redacted]

Reviewer's comments: The remainder of the post-approval stability protocol should be reviewed by OBP.

Satisfactory

Stability data

Endotoxin levels during stability at 2 to 8°C are < [Redacted] EU/mg ([Redacted] EU/mg) and sterility and CCI results conformed with the specification at all tested points.

Reviewer's comments: Stability data other than CCI, sterility and endotoxin should be reviewed by OBP.

Satisfactory

3.2.A.1 FACILITIES AND EQUIPMENT

Reslizumab drug product is manufactured by [Redacted] a multi-product contract manufacturing facility.

Reslizumab drug product is manufactured [Redacted]

[Redacted] The diagrams [Redacted] are provided and are adequate. [Redacted]

FDA question (August 23, 2015): Please provide the type of products filled [Redacted]

[Redacted]

Firm's response in September 11, 2015 amendment (Sequence 013):

(b) (4)

Satisfactory

CGMP Status

Please see Panorama

Conclusion

- I. The drug product section of this BLA was reviewed from a product quality microbiology perspective and recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by the OBP reviewer.
- III. The inspection of the drug product manufacturing site, [REDACTED] ^{(b) (4)} was waived.

Lakshmi
Narasimhan -S

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CMC Microbiology Deficiencies for BLA 761033/0 reslizumab**Information Requests sent****May 11, 2015****I. Labeling**

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 25°C (77°F), 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 25°C. 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.

II. The following qualification information and data in Appendix 3.2.A.1 should be moved to section 3.2.P.3:**III. A summary of the EM program is described in Appendix 3.2.A.1. Please move the information to section 3.2.P.3.5.****IV. Media fill simulation information in Appendix 3.2.A.1 should be moved to section 3.2.P.3.****V. Provide the details of bioburden testing and method qualification summary data from 3 formulated bulk drug product lots.****VI. Please provide information and summary data for the rabbit pyrogen test of Reslizumab in conformance to 21CFR610.13 (b). The rabbit pyrogen test should be done at least once with 3 lots of finished drug products to demonstrate that the product does not contain pyrogenic substances other than bacterial endotoxin.****VII. Low endotoxin Recovery**

Please provide evidence that the drug product formulation does not interfere with endotoxin recovery in the LAL test. Conduct spiking studies on the undiluted drug product with known amount of endotoxin and simulate the worst-case hold conditions to evaluate endotoxin masking over time. The studies should be conducted using containers of similar composition as those used for the drug product.

August 23, 2015

I. Container closure integrity (CCI) test

Microbial ingress test

1. In the microbial ingress CCI test method used for testing the vials after the container closure operational qualification, it is not clear (b) (4)

Clarify (b) (4) used for the (b) (4) study.
2. It is not clear if the (b) (4) study was performed using worst case conditions. Please submit the (b) (4) study report for microbial ingress CCI test method for the reslizumab primary container system. Report should include the following information: Description of the test including critical parameters (initial and final concentration of challenge organism, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge), number of positive, negative controls and test units used in the study, preparation of positive and negative control and sensitivity of the method (LOD) as a function of breach size. In addition, describe how the final concentration of challenge organism was verified.
3. Clarify if this (b) (4) CCI study was performed using the media filled vials representing commercial reslizumab primary container system.

Dye ingress test

4. Please clarify if negative controls are included in the dye ingress test and if they are exposed to the test conditions.
5. Please submit the dye ingress CCI test method qualification report for the reslizumab primary container system with the following information: Description of the test including critical parameters (concentration of dye, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge and dye), drug product lots used and number of positive, negative controls and test units used in the study, preparation of positive and negative controls, clarify if negative controls are exposed to the test conditions and sensitivity of the method (LOD) as a function of breach size. In addition, describe in detail how the LOD of the test was calculated.
6. Please provide the correlation between the dye ingress test and microbial ingress test with respect to challenge conditions and breach size.

Capping Force

7. Please provide CCI test results obtained using with worst-case crimping process parameters to qualify the container closure system for reslizumab drug product

II. Drug product manufacturing process

8. [Redacted] (b) (4)

III. Process Validation

Hold time

9. Please indicate the temperature used to qualify the process hold conditions and also clarify if the temperatures used are representative of those used in manufacturing.

10. Please submit hold time data from manufacturing scale [Redacted] (b) (4) of the reslizumab DP.

(b) (4) Validation
11. Please clarify [Redacted] (b) (4)

12. Include a comparison of the validation and current production parameters. [Redacted] (b) (4)

Media Fill

13. The summary of current media fill validation (Table 20, 21 and 22) state [Redacted] (b) (4)
Please clarify what you mean [Redacted] (b) (4)

14. For the media fills, Batch No. 921389, 921453, and 921390
a. please provide the duration of fill
b. Compare the media fill parameters with the routine product fill parameters

(b) (4)
15. Please provide the validation information and summary data from three recent runs [Redacted] (b) (4)
a. Include [Redacted] (b) (4)
b. Include a comparison of the validation and production operating parameters [Redacted] (b) (4)

16. Please provide the validation information and summary data from three recent runs [Redacted] (b) (4)
a. Ensure that the information includes [Redacted] (b) (4) parameters used.
b. Include [Redacted] (b) (4)

- c. Include a comparison of the validation and production operating parameters (b) (4)

(b) (4)

17. Please provide the information and summary data of the most recent (b) (4) qualification runs

18. Include a comparison of the validation and production operating parameters of the (b) (4) process.

Justification of Specification

19. The proposed commercial specification endotoxin limit \leq (b) (4) EU/mg does not provide any safety factor. Additionally, the 0.9% sodium chloride injection USP used to dilute the DP for intravenous infusion may also add to the level of endotoxin. Your data indicate that the endotoxin levels at release and during stability at 2 to 8°C are $<$ (b) (4) EU/mg. Please tighten the current reslizumab DP release endotoxin specification to provide a safety margin.

Stability

20. We recommend that a container closure integrity test be performed (b) (4)

Facilities and equipment

21. Please provide the type of products filled (b) (4)

FDA comments to the Firm's response (amendment in Sequence 0003)

22. Please submit the report providing the information and result summary data of rabbit pyrogen testing performed with 3 lots of finished drug products of reslizumab.

October 19, 2015

I. Validation of Analytical procedures

1. Endotoxin test:

a. Please provide the rationale for characterizing the endotoxin assay method validation (b) (4)

2. Sterility test

a. It is not clear whether the sterility test method qualification was performed with drug product manufactured by the commercial process (b) (4) Please respond to the following comments.

i. Section 3.2.P.5.3 states that the sterility test method validation was conducted on two reslizumab drug product batches (10-001036 and 10-000862) while the Report 07-02-F002-24.0 "Determining Bacteriostasis/Fungistasis Activity of Bulk and Finished Products" states (b) (4) used in the method verification study and Report 07-02-F002-25

provides the sterility method verification results from DP batch number 916273. Please clarify the discrepancy.

ii. *Please clarify if the sterility test method qualification studies were performed with commercial manufacturing DP lots.*

iii. *Please clarify if the method verification results provided in Report 07-02-F002-24.0 are from the DP (b) (4)*

b. *Please provide details of the sterility test method qualification (b) (4)*

3. Bioburden

a. *Report (b) (4)-103, "Method validation-bioburden" provides the bioburden method validation results from batch Numbers 917774, 918503, and 918504 while Section 3.2.P.5.3 provides the method validation results from batches 11-00001, 11-002802 and 11-002803. Please clarify the discrepancy.*

II. Process Validation

(b) (4)

III. FDA comments to the response in amendment dated September 11, 2015 in sequence # 0013:

Container closure integrity (CCI) test

a. *Please submit the protocol used to execute the (b) (4) study for container closure integrity testing using Microbial Ingress and Liquid Dye Ingress Challenges.*

b. *The (b) (4) study was performed (b) (4)*

Please clarify.

c. *The dye ingress CCI test method qualification study was performed (b) (4)*

(b) (4)

(b) (4)

Drug product manufacturing process

Please update sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA application to reflect the implementation of (b) (4) bioburden and endotoxin sampling (b) (4)

Process Validation1. (b) (4) Validation

It is not clear why the (b) (4) validation study was performed at (b) (4) °C instead of the routine production temperature of (b) (4) °C. Please clarify whether the drug product has a bactericidal effect on the challenge organism at (b) (4) °C. Provide justification for performing the study at (b) (4) °C and provide viability data for the challenge organism in the drug product at (b) (4) °C, if available.

2. Media Fill

a. Please submit the media fill data and information of the recent media fill (lot 921884) including the following information: date of filling, filling speed, fill volume, total number of units filled, number of non-integral units, number of (b) (4) contaminated units, growth promotion results, and duration of media fill simulation

b. Provide a summary of the environmental monitoring data obtained (b) (4) lot 921884.

c. Compare the media fill parameters with the routine product fill parameters including fill speed and duration of the fill.

3. (b) (4)

It is not clear (b) (4) Please clarify.

4. Rabbit pyrogen testing

Please clarify if the rabbit pyrogen test studies were performed with commercial manufacturing DP lots.

October 29, 2015

Please update sections 3.2.P.5.1 and 3.2.P.5.6 of the BLA application with the tightened endotoxin specification of (b) (4) EU/mg.

November 18, 2015***I. Drug product manufacturing process***

Establish (b) (4) bioburden and endotoxin limits (b) (4)

II. Process Validation

a. (b) (4) Validation

You have stated (b) (4)

Please justify the acceptability of executing microbial retention validation study for (b) (4) at (b) (4) °C instead of the routine production temperature. It is not clear that the microbial retention study considered the effect of worst case temperature (b) (4)

b. Media Fill

A LOA for (b) (4) Type V DMF (b) (4) was provided to review the environmental monitoring data for media fill lot # 921884. The provided DMF number (b) (4) is incorrect; please provide the correct number for the (b) (4) Type V DMF and indicate the pages where the information is located.

c. (b) (4)

Please provide a comparison of validation and routine production run parameters (b) (4) used for reslizumab manufacturing.

III. Validation of Analytical procedures

Sterility

Sterility method qualification has been completed using only two drug product lots. Please submit the sterility test method qualification information and results from study performed using an additional commercial drug product lot.

November 24, 2015

Please update sections 3.2.P.5.1 and 3.2.P.8.2 of the BLA application that the container closure integrity test will be performed (b) (4) as described in your communication dated September 11, 2015.