

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125526Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



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

Date: October 15, 2015
To: Administrative File, STN 125526
From: Candace Gomez-Broughton, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Patricia Hughes, Ph.D. Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologic License Application
US License: 1727
Applicant: GlaxoSmithKline LLC
Facility: DP: GlaxoSmithKline Manufacturing S.p.A., Parma, Italy (FEI=3002807114)
Product: Nucala™ (mepolizumab)
Dosage: Lyophilized powder for reconstitution and subcutaneous injection, 100 mg/vial
Indication: Treatment of patients with severe eosinophilic asthma
Due date: November 4, 2015

Recommendation: The drug product section of BLA 125526, as amended, is recommended for approval from a microbiology product quality perspective with the following Post-Marketing commitment:

To qualify the bioburden test at the (b) (4) in the drug product manufacturing process using a sample volume of 100 mL and to implement a (b) (4) bioburden limit of (b) (4)/100 mL. The qualification and implementation of the bioburden test will be submitted as a CBE-0 supplement.

INTRODUCTION

This review covers the product quality microbiology of the drug product final lyophilized product as presented in BLA sections 3.2.P. The product quality microbiology review for the drug substance was completed by Reyes Candau-Chacon, Ph.D. included in the CMC integrated review memo.

ASSESSMENT

P Drug Product

P.1 Description and Composition of the Drug Product

The mepolizumab drug (DP) is a white lyophilized cake which consists of (b) (4) mg/mL mepolizumab, (b) (4) sodium phosphate dibasic heptahydrate, (b) (4) sucrose (b) (4), and (b) (4) polysorbate 80 (b) (4) at pH 7.0. The drug product is filled in 10 mL Type I glass vials that are

sealed with gray (b) (4) rubber stoppers and aluminum overseals with red flip-off caps. The drug product is reconstituted with 1.2 mL of sterile water for injection (WFI) which is not supplied with the finished product. The drug product is intended for administration by subcutaneous injection.

P.2 Pharmaceutical Development

P.2.5 Microbial Attributes

Mepolizumab is a preservative free sterile drug product. Sterility assurance is achieved through (b) (4), controls for components, equipment, the processing environment, microbial and microbial-related testing (sterility and endotoxin) of the finished drug product. (b) (4) bioburden is monitored (b) (4). The sterility test is performed at release and at the end of shelf-life for drug product batches placed on stability. For drug product placed on stability, container closure integrity testing is completed in lieu of sterility at intermediate time points. Sterility testing is performed in accordance with USP <71>.

P.2.5.1.1 Bacterial Endotoxin Test

Bulk drug substance (BDS) and drug product (DP) are tested for endotoxin levels at release with an acceptance criterion of \leq (b) (4) EU/mg. In order to meet CFR 610.13(b) requirements, the rabbit pyrogen test and the limulus amoebocyte lysate method were used simultaneously to detect and quantify bacterial endotoxin. The study was completed using three developmental batches at 250 mg/vial (5003, 5004, and 6001) and three commercial batches at the 100 mg/vial concentration (3508, 33509, and 4501). Results from each lot met the acceptance criterion of \leq (b) (4) EU/mg and also passed the rabbit pyrogen test. Each of the developmental batches had endotoxin levels of $<$ (b) (4) EU/mg and the commercial batches has endotoxin levels of (b) (4) EU/mg. These results support the use of the Kinetic Quantitative Chromogenic Limulus amoebocyte lysate (LAL) method *in lieu* of the rabbit pyrogen test for mepolizumab drug product release at 100 mg/vial.

P.2.5.1.1 Container Closure Integrity Test

Container closure integrity is evaluated annually as part of the stability program between the initial time point and end of shelf-life *in lieu* of sterility testing. The container closure integrity test method is described in Section P.5.2. Validation of the method is described in section P.5.3.

P.3 Manufacture

P.3.1 Manufacturers

The table below provides a list of mepolizumab drug product manufacturing sites and the operations that take place in each.

Facility	Operations
GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana, 90 43056 San Polo di Torrile, Parma, Italy	DP manufacturing, release, stability, labeling, primary and secondary packaging
Biopharmaceutical Central Testing Laboratories	Release, stability testing

GlaxoSmithKline Medicines Research Centre Gunnels Wood Road Stevenage Hertfordshire SG1 2NY UK	
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Reviewer comment: Facilities will be reviewed by the Division of Inspectional Assessment in a separate memo.

P.3.2 Batch Formula

The mepolizumab drug product is presented as a lyophilized powder at a concentration of 100 mg/vial. The formulation consists of (b) (4) mg/mL mepolizumab, (b) (4) sodium phosphate dibasic heptahydrate, (b) (4) sucrose (b) (4), and (b) (4) polysorbate 80 (b) (4) at pH 7.0.

The representative batch size for commercial production ranges from (b) (4) kg which produces a theoretical batch that varies between approximately (b) (4) vials depending on the (b) (4). There are (b) (4) to DP manufacturing.

P.3.3 Description of Manufacturing Process and Process Controls

Mepolizumab drug product manufacturing process is completed in (b) (4) GlaxoSmithKline (GSK) facility in Parma, Italy. Drug product manufacturing consists of the following unit operations:

(b) (4)

(b) (4)

(b) (4)

- (b) (4) bioburden: (b) (4) mL

- (b) (4) endotoxin: (b) (4) EU/mg
- (b) (4) integrity test

(b) (4)

Reviewer Question: Please justify the (b) (4) bioburden limit of (b) (4) mL. Current industry practice is to set the pre-sterile filtration limit to (b) (4)/100 mL.

Sponsor Response: The (b) (4) bioburden acceptance criterion of (b) (4) mL for a (b) (4) mL sample volume is justified as follows:

(b) (4)

Reviewer comment: The sponsor's justification for the (b) (4) bioburden is inadequate. Therefore the sponsor has agreed to the following Post-Marketing Commitment:

To qualify the bioburden test at the (b) (4) step in the drug product manufacturing process using a sample volume of 100 mL and to implement a (b) (4) bioburden limit of (b) (4)/100 mL. The qualification and implementation of the bioburden test will be submitted as a CBE-0 supplement.

SATISFACTORY

P.3.4 Control of Critical Steps and Intermediates

The microbiological critical process parameter is (b) (4) must pass the integrity test by meeting the limits set based on the supplier validation studies for mepolizumab.

There are (b) (4) in the mepolizumab DP manufacturing.

P.3.5 Process Validation and/or Evaluation

The sponsor used a 3-stage lifecycle approach to process validation which consisted of the following:

- Stage 1 – Process Design (Development): developmental, clinical, and scaled-up engineering product batches were used to develop product and process knowledge
- Stage 2 – Process Qualification or Process Performance Qualification (PPQ): manufacturing process evaluated for the ability to consistently manufacture drug product which meets specification
- Stage 3 – Continued Process Verification: activity intended to provide lasting assurance that the process remains in control

P.3.5.2 Process Performance Qualification (PPQ)

P.3.5.2.1 Batch Details

A summary of the batches used in the PPQ studies are summarized in the table below.

Lot Number	Manufacturing Date ¹	Batch Size (kg)	Corresponding BDS Lot Number
3507	(b) (4)	(b) (4)	0000560167 (MDS2 -T0413007)
3508	(b) (4)	(b) (4)	0000560219 (MDS2 -T0413008)
3509	(b) (4)	(b) (4)	0000562431 (MDS2 -T0413009)

Note:

1. The manufacturing date corresponds to the start of the lyophilization cycle.

Acceptance criteria for PPQ studies are as follows:

- Minimum of 3 consecutive and successful batches
- Defined controls must be maintained within their acceptance criteria
- Deviations must not have negative effect on study effectiveness
- Process consistency and performance must be confirmed by evaluation of all monitored parameters
- PPQ batch results must meet acceptance criteria
- Batches must meet release specifications

P.3.5.3 Process Validation Studies and Results

P.3.5.3.2.2 Microbial Hold Time from Beginning of Preparation to (b) (4)

Validation studies were completed to support the maximum hold time for the BDS. Samples were collected (b) (4). Hold time from the start (b) (4) to the end of (b) (4) was assessed for microbial control.

Samples were tested for bioburden and endotoxin and met the acceptance criteria. Bioburden results were (b) (4) mL for all batches at each test point (acceptance criteria: ≤ (b) (4) mL). Endotoxin results were < (b) (4) EU/mg for all batches at each test point (acceptance criteria: ≤ (b) (4) EU/mg). The sponsor states that these results support a maximum possible hold time of (b) (4) in the manufacturing instructions for BDS (b) (4).

Reviewer Question: Provide actual hold times used in the microbiological hold time validation studies and the validated hold time.

Sponsor Response: The sponsor provided the start of preparation and sample collection times

used in the hold time validation studies. Based on the results of the validation studies, the most conservative hold time among the three runs was considered. The maximum allowable microbial hold time was set at ^(b)₍₄₎ hours in the manufacturing instructions for the mepolizumab drug product. Table 1 of the sponsor's response summarizes the hold time used in the validation studies and is shown below.

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

SATISFACTORY

P.3.5.6 Shipping Validation

The DP packaging, shipping procedures, and processes for the mepolizumab shipment were validated based on the successful completion of American Society for Testing and Materials (ASTM) distribution and analytical testing. Components used to package the vials met acceptance criteria and are suitable for their intended use in ground, sea and air transport. Results from the shipping validation studies showed no vial leaks, damaged vial closures, or breaks in the vial glass. Therefore shipping does not adversely affect product quality.

GSK uses temperature controlled trucks and temperature control systems for air and sea shipments. The sponsor intends to monitor the temperature of each DP shipment and mandates the use of suitable validation monitors. Shipments will include at least one temperature monitor which will record the temperature data for the duration of the shipment.

Reviewer comments: Results from validation studies collectively show that the manufacturing parameters selected for mepolizumab DP manufacturing are adequate to support commercial production.

P.5 Control of Drug Product

P.5.1 Specification(s)

Specifications related to microbial quality are listed below:

- Endotoxin: \leq (b) (4) EU/mg
- Sterility: pass
- Container closure integrity (stability): pass

P.5.2 Analytical Procedures

(b) (4)



Endotoxin

Bacterial endotoxin is tested for using the kinetic chromogenic method in accordance with USP <85>. Kinetic Quantitative Chromogenic Limulus Amebocyte Lysate (KQCL) assay is used for testing the DP samples. The assay consists of the test sample at the qualified dilution, the control

(b) (4)



P.5.3 Validation of Analytical Procedures

Qualification of Analytical Method for Sterility Testing

(b) (4)

Acceptance criteria were met and are summarized in the table below and copied from the submission.

Challenge Organism (media)	Acceptance Criteria	Batch 7001	Batch 7001	Batch 6001
		Result	Result	Result
<i>B. subtilis</i> ATCC 6633 (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>C. albicans</i> ATCC 10231 (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>A. niger</i> ¹ ATCC 16404 (TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>C. sporogenes</i> ATCC 19404 (FTM)	Growth in (b) (4) days	Pass	Pass	Pass
<i>C. sporogenes</i> ATCC 11437 (FTM)	Growth in (b) (4) days	Pass	Pass	Pass
<i>S. aureus</i> ATCC 6538 (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>P. aeruginosa</i> ATCC 9027 (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>E. coli</i> ATCC 8739 (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>M. lylae</i> (environmental isolated) (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
<i>B. coagulans</i> (environmental isolated) (FTM and TSB)	Growth in (b) (4) days	Pass	Pass	Pass
Inoculum Challenge Level	(b) (4) Colony Forming Units (CFU)	Pass	Pass	Pass
Product Control:	Sterile	Pass	Pass	Pass
Negative Controls for the TSB and FTM media were negative.				

Note:

1. Currently referred to as *Aspergillus brasiliensis* ATCC 16404

Qualification of Analytical Method for Bacterial Endotoxin-Kinetic Chromogenic

Qualification studies were completed to demonstrate that the kinetic chromogenic method is adequate to measure endotoxin in mepolizumab DP samples. Also, a spiking study was completed to show the effect of hold time on endotoxin recovery in reconstituted and undiluted mepolizumab.

Three batches of mepolizumab DP were used in the qualification studies (5003, 5004, and 5005). Each was tested three times. In the inhibition/enhancement studies, the samples are diluted not to exceed the maximum valid dilution (MVD) which is (b) (4). The qualified sample dilution is cannot be above the MVD and when spiked with a known amount of endotoxin standard, value is within the range of (b) (4)% for three batches. The qualified test dilution is 1:20. Results from the spiking study met the acceptance criteria confirming that the drug product does not enhance or inhibit endotoxin recovery. The results are summarized in the table below.

Table 1 Summary of Qualification Results

Total Aerobic Microbial Count (TAMC) on TSA plates incubated at 30-35°C					
Test Sample	Challenge Organism	Organism Type	Sample Percent Recovery		
			Batch 5001 - dev ²	Batch 5002 - dev ²	Batch 5001 ² (b) (4)
Mepolizumab DP (250 mg/vial configuration) (b) (4)	ATCC 6633 <i>B. subtilis</i>	Gram positive rod			
	ATCC 6538 <i>S. aureus</i>	Gram positive cocci			
	ATCC 9027 <i>P. aeruginosa</i>	Gram negative rod			
	ATCC 16404 <i>A. niger</i> ¹	Mold			
	ATCC 10231 <i>C. albicans</i>	Yeast			
	ATCC 8739 <i>E. coli</i>	Gram negative rod			
	Environmental Isolated – <i>S. cohnii</i>	Gram positive cocci			
	Environmental Isolated – <i>B. subtilis</i>	Gram positive rod			
Inoculum Challenge Level: 10 – 100 cfu					
Negative Controls for the TSA media were negative.					

Notes:

1. Currently referred to as *Aspergillus brasiliensis* ATCC 16404
2. DP batch is identified from which the in process material was derived.

The configuration material of the 250 mg/vial and 100 mg/vial presentations is equivalent. Therefore, no additional studies using the 100 mg/vial configuration are required.

P.5.4 Batch Analysis

The sponsor submitted data for nine batches manufactured using the commercial process (MDP2, 100 mg/vial). This included three drug product process performance qualification (PPQ) batches (3507, 3508, and 3509). The sponsor has also provided data from 13 batches manufacturing using the MDP1 (250 mg/vial) process and 14 batches manufactured using the pilot process.

All batches were tested against the specifications in place at the time of testing. Results for endotoxin and sterility met specification for all batches.

P.5.6 Justification of Specification

P.5.6.3.16 Endotoxin

Endotoxin is detected using the Kinetic Quantitative Chromogenic Limulus Amebocyte Lysate method. The maximum allowed endotoxin limits were determined for a recommended dose of 100 mg is (b) (4) EU/mg for a 70 kg person. For individuals who are ≥ 12 years old (using the 50th percentile body weight of 40 kg) the maximum allowed endotoxin limit is (b) (4) EU/mg. The specification of ≤ (b) (4) EU/mg was set based on manufacturing history and is significantly below the maximum allowable levels for adults and adolescents. In addition, the endotoxin level for drug product development and commercial batches has consistently been ≤ (b) (4) EU/mg.

P.5.6.3.17 Sterility

The mepolizumab drug product must be sterile at release as specified in the EP 2.6.1, USP <71> and 21 CFR 610.12. Sterility testing is completed at release and at expiry.

P.5.6.3.18 Container Closure

CCIT is determined using the dye immersion test. The acceptance criterion is expressed “Passes Test”. DP is tested for container closure integrity as part of the stability protocol at the initial time point through expiry.

Reviewer comment: The specifications for mepolizumab drug product have been adequately justified.

P.7 Container Closure System

The mepolizumab drug product is filled in to Type 1 clear glass vials, sealed with a (b) (4) rubber stoppers. The vials are sealed with aluminum overseals with flip-off caps.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Stability data currently available support the claim that the Mepolizumab drug product will remain within specification for up to 24 months when stored at the recommended temperature of $\leq 25^{\circ}\text{C}$. The data available in this section include the following:

- Long term stability data for drug product stored at for 60 months (250 mg/vial) and 18 months (100 mg/vial) at 5°C and $25^{\circ}\text{C}/60\% \text{RH}$.
- Accelerated stability data for drug product stored for 6 and 12 months (250 mg/vial) and 18 months (100 mg/vial) at $30^{\circ}\text{C}/65\% \text{RH}$.
- Accelerated stability data for 100 mg/vial drug product stored for 18 months at $30^{\circ}\text{C}/35\% \text{RH}$ and $30^{\circ}\text{C}/75\% \text{RH}$.

Mepolizumab drug product stability was evaluated at $5^{\circ}\text{C}\pm 3^{\circ}\text{C}$ and at $25^{\circ}\text{C}/60\% \text{RH}$ to support a commercial shelf life of 24 months when stored at $\leq 25^{\circ}\text{C}$ protected from light. Stability was also evaluated under the following stressed conditions:

- $30^{\circ}\text{C}/65\% \text{RH}$
- $30^{\circ}\text{C}/35\% \text{RH}$
- $30^{\circ}\text{C}/75\%$
- $40^{\circ}\text{C}/75\% \text{RH}$

All results for container closure integrity and sterility met the specifications.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

(b) (4)

SATISFACTORY

CONCLUSION

- I. The drug product section of the BLA is recommended for approval from a sterility assurance and microbiology product quality perspective with the following Post-Marketing Commitment:

To qualify the bioburden test at the [REDACTED]^{(b) (4)} in the drug product manufacturing process using a sample volume of 100 mL and to implement a [REDACTED]^{(b) (4)} bioburden limit of [REDACTED]^{(b) (4)}/100 mL. The qualification and implementation of the bioburden test will be submitted as a CBE-0 supplement.

- II. CMC product specific information and data should be reviewed by the OBP/DMA reviewer.
- III. No additional inspectional follow-up items were identified.

FDA Information Request for STN 125526/0 Microbial Quality

Information Request Sent March 4, 2015

1. P.3.3 Description of Manufacturing Process and Process Controls
 - a. Table 1 lists Microbial safety as a critical quality attribute affected at the [REDACTED] (b) (4). However, endotoxin is not monitored at this step. We recommend that [REDACTED] (b) (4) endotoxin testing be implemented at this step in the process.
 - b. Please justify the [REDACTED] (b) (4) bioburden limit of [REDACTED] (b) (4). Current industry practice is to set the [REDACTED] (b) (4) limit to [REDACTED] (b) (4)/100 mL.
2. P.8.1 Stability Summary and Conclusion
 - a. We recommend that the container closure integrity test be completed in lieu of the sterility test for stability at the initial time point and annually until expiry. Please revise the stability protocol accordingly.

Information Request Sent July, 8, 2015

P.3.5.3 Process Validation Studies and Results

1. Provide actual hold times used in the microbiological hold time validation studies and the validated hold time.
2. With regard to the [REDACTED] (b) (4) validation studies, provide the following:
 - a. Number of runs included in the validation studies.
 - b. Maximum [REDACTED] (b) (4) speed used in the validation studies.
 - c. Maximum and minimum [REDACTED] (b) (4) forces used in the validation studies.
 - d. Description of the controls used in the study.
 - e. Description of the quantitative dynamic dye test used to assess the integrity of the sealed vials, indicate if the method has been validated and submit the method validation report.
3. Indicate how [REDACTED] (b) (4) validation parameters differ from those used during routine operations
4. With regard to the [REDACTED] (b) (4) validation studies, please provide the following.
 - a. Justification for using [REDACTED] (b) (4) vials as worst case in the [REDACTED] (b) (4) validation studies.

- b. Report for the (b) (4) endotoxin challenge and (b) (4) thermal trials.
5. With regard to the (b) (4) validation, microbial challenge and thermal challenge studies should be done using three runs. In addition, the validation should be relevant to equipment and components used in mepolizumab drug product manufacturing. Please submit the study reports which should include the following:
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)
 - d. (b) (4)
 - e. (b) (4)
 - f. (b) (4)
6. Indicate if (b) (4) used in the (b) (4) validation studies is used in mepolizumab manufacturing and provide the most recent requalification report.
7. With regard to the lyophilizer (b) (4) validation studies, provide the following:
 - a. Clarify which lyophilizers are used in mepolizumab production.
 - b. Provide the study reports from initial qualification studies as well as most recent re-qualification using thermal and microbial challenge trials.
8. With regard to the (b) (4) studies, identify the two environmental isolates used in the growth promotion studies.
9. Please provide the most recent (b) (4), number of rejections, deviations, and a summary of the environmental monitoring data.
10. Please address the failed endotoxin recovery result of (b) (4) % in the DP spiking and hold study completed using CSE.

Information Request Sent September 14, 2015

Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. In the information request sent to the sponsor on 04 Mar 2015 the sponsor was asked to justify the (b) (4) bioburden limit of (b) (4). The sponsor's justification for the (b) (4) bioburden (b) (4) provided in Sequence 0016 is inadequate (b) (4) samples collected after the (b) (4) are assumed to have (b) (4)

(b) (4)/100 mL, which provides no useful insight into the microbial control of the manufacturing process and cannot be considered (b) (4) samples. The (b) (4) bioburden limit should be changed to (b) (4)/100 mL. In addition, (b) (4) samples should be collected prior to the (b) (4). Please amend the BLA accordingly.



Information Request Sent September 30, 2015

1. Please respond to the following comments regarding (b) (4) of the (b) (4) which is composed of (b) (4)
 - a. Provide a copy of the Certificate of Analysis for the (b) (4)
 - b. Submit the validation report for the (b) (4) process used to sterile the (b) (4) completed by the supplier
 - c. Describe the leak integrity test performed by the supplier, indicate the test method sensitivity in terms of detectable leak size, and summarize the method validation data.

2. In Section 3.2.P.3.5.4.5.2.2 ^{(b) (4)}, validation studies for the ^{(b) (4)}

[Redacted]

a.

[Redacted] ^{(b) (4)}

b. Dates for which these studies were conducted

SIGNATURES

Candace Y. Gomez-broughton -S

Digitally signed by Candace Y. Gomez-broughton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2000640207,
cn=Candace Y. Gomez-broughton -S
Date: 2015.10.15 14:47:14 -04'00'

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Food and Drug Administration
Center for Drug Evaluation and Research
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Date: July 10, 2015
To: Administrative File, STN 125526/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1727
Applicant: GlaxoSmithKline, LLC
Facilities: GlaxoSmithKline LLC, 893 River Road, Conshohocken, PA 19428 (FEI 3004055938)
Product: NUCALA (mepolizumab, SB-240563)
Dosage: Vials containing 100 mg powder for subcutaneous injection after reconstitution to be administered every 4 weeks
Indication: [REDACTED] (b) (4)
Due date: November 4, 2015

Recommendation for Approvability: The drug substance part of BLA 125526 is recommended for approval from a microbial control and microbiology product quality perspective

Review Summary

GlaxoSmithKline, LLC has submitted BLA 125526 to license mepolizumab drug substance and drug product and their manufacturing processes.

BLA 125526 was submitted in eCTD on November 04, 2014. This review contains the assessment of the manufacturing process of mepolizumab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Gomez-Broughton.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
February 11, 2015	1 to 9	0012	March 9, 2015
	7c and 7d	0030	June 10, 2015
April 9, 2015	2c, 3a, 5c	0025	May 14, 2015
	2c, 2d	0034	June 29, 2015

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

Mepolizumab is a recombinant humanized IgG1 monoclonal antibody produced in (b) (4) CHO cells (b) (4). Mepolizumab binds and neutralizes soluble IL-5, resulting in inhibition of the IL-5 signaling. (b) (4)
 (b) (4),
 resulting in a molecular weight of 149 KDa.

Satisfactory

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of mepolizumab drug substance:

- GlaxoSmithKline LLC, 893 River Road, Conshohocken, PA 19428; (b) (4)
 (b) (4)
 FEI 3004055938
- Biopharmaceutical Central Testing Laboratories, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK; (b) (4)
 (b) (4)
 FEI 3009763376
- (b) (4)
- (b) (4)

Reviewer comments:

Refer to the cGMP status section of this review for the compliance status of GlaxoSmithKline LLC, Conshohocken, PA.

S.2.2 Description of the Manufacturing Process and Process Controls

S.2.2.1

(b) (4)

S.2.2.2

FDA Question 4.a

Justify the bioburden and endotoxin acceptance criteria used to support microbial control of (b) (4).

Sponsor's Response in amendment 0012

The sponsor indicates that the acceptance criteria used to support microbial control of the (b) (4) is aligned with the limits of the (b) (4).

Satisfactory



Satisfactory

S.2.5.3 Shipping Validation

Shipping validation was conducted using simulated and real life shipping studies.

The simulated study included maximum and minimum load. The minimum load consisted in a single (b) (4) and the maximum load consisted in (b) (4).

The containers were packed according to the SOP and held at temperature above RT. Data-loggers were placed within the shipment as indicated in Figure 4; the temperature was recorded to assess the time at which the packing configuration was able to maintain the temperature at (b) (4) °C. The results are shown in Table 6.

Table 6: Results of simulated shipping

Load	Time < (b) (4) °C	External Temperature (b) (4)
Minimum	(b) (4)	(b) (4)
Maximum	(b) (4)	(b) (4)

The real time shipping study was conducted using only the maximum load in 3 independent runs. The bottles were packed according to the SOP, data-loggers were placed as indicated in Figure 3, and the shippers were sent to the DP manufacturing facility. Upon receipt, the shipping time was recorded, bottles were unpacked and stored, and data-loggers were removed and downloaded. Table 7, duplicated from Table 53, section 3.2.S.2.5 of the BLA summarizes the results of the validation.

Table 7: Results of shipping validation

Acceptance Criteria	Shipment			
	1	2	3	
				(b) (4)
				(b) (4)
				(b) (4)

Reviewer's Comment:

Although the simulated study showed that the maximum load was able to sustain the required temperature for less time than the minimum load, suggesting that the maximum load is worst-case, the external temperature for the maximum load was higher than for the minimum load. Therefore, a justification for using only maximum load for the shipping validation studies is necessary.

FDA Question 5.a

Indicate the external temperature during the real time shipping validation study.

Sponsor's Response in amendment 0012

The exterior minimum temperature for the three shipments was between (b) (4) °C; the exterior maximum temperature for all shipments was between (b) (4) °C.

Satisfactory

FDA Question 5.b

Indicate if the location of the data-loggers for the maximum load study during the simulated shipping is the same as indicated in Figure 73 of section 3.2.S.2.5.

Sponsor's Response in amendment 0012

The sponsor indicates that the data-logger placement for the simulated shipping studies (IOQ) are different than the location for the real time validation study (PQ). A diagram showing the location of the data-loggers in the simulated shipping is included in the amendment and it shows three data-loggers (b) (4)

Satisfactory

FDA Question 5.c

Justify not using a minimum load for the real-life shipping validation study.

Sponsor's Response in amendment 0012

The results from the simulated studies show that the maximum load (b) (4) is worst-case. The maximum load was within the acceptance criterion ((b) (4) °C) for (b) (4) hours; the minimum load was within acceptance criterion for (b) (4) hours. One error identified in Table 53 of section 3.2.S.2.5 was corrected to indicate that Study 1 consisted of 2 shippers, one with 3 BDS containers and the other with 2 BDS containers.

Reviewer's comment to sponsor's response to question 5.c submitted in amendment 0012

Please submit summary results of maximum and minimum load from the simulated shipping studies (IOQ).

Sponsor's Response in amendment 0025

Results from the maximum and minimum load of the simulated shipping are included in the amendment. The results confirm that the maximum load is worst-case scenario for temperature.

Satisfactory

S.2.6 Manufacturing Process Development

Reviewer Comment:

This section is deferred to OBP

S.3 Characterization

Reviewer Comment:

This section is deferred to OBP

S.4 Control of Drug Substance

S.4.1 Specifications

Specifications for Mepolizumab DS microbial quality are:

- Bioburden: (b) (4)
- Bacterial endotoxin: (b) (4) EU/mg

(b) (4) tests conducted on (b) (4) bulk as part of batch release include:

- Bioburden: (b) (4)
- Mycoplasma: AC: Not detected
- In vitro adventitious agents: AC: Not detected

Reviewer's Comment:

Only bioburden and endotoxin are reviewed here. The sponsor agreed in amendment 0012, response to question 2.d to (b) (4) the bioburden (b) (4) bulk test volume to (b) (4) mL.

Satisfactory

S.4.2 Analytical Procedures

Bioburden Method

The bioburden test is conducted according to USP <61>, Ph. Eur. 2.6.12.

Endotoxin method

Bacteria endotoxin is determined using the LAL Kinetic Chromogenic method according to USP <85> and Ph. Eur. 2.6.14.

FDA Question 6.a

Describe the bioburden and endotoxin methods for DS release, (b) (4) bulk (only bioburden), and (b) (4) samples. Include sample volume, dilution factor if applicable, and bioburden sample incubation conditions.

Sponsor's Response in amendment 0012

Bioburden is determined using the membrane filtration method for all samples (b)(4) and release for upstream and downstream processes). For the (b)(4)

Bacterial endotoxin is determined using the LAL Kinetic Chromogenic Method (KCM) with samples and controls tested in duplicates; test samples are spiked to show endotoxin recoveries. The standard curve includes 5 points to cover the endotoxin level expected in the sample; lysate sensitivity is (b)(4) EU/mL. Acceptance criteria include the USP assurance criteria for the standard curve, the USP acceptance criteria for the test, and coefficient of variation (%CV) (b)(4)% between replicates of the standard curve and between replicates of the samples and PPC. Table 2 of the amendment includes the validated test dilution for (b)(4) and BDS.

Satisfactory

FDA Question 6.b

Clarify if the reported bioburden in the CofA result will be the sum of the TAMC + TYMC and will be specified as such.

Sponsor's Response in amendment 0012

The bioburden results are reported separately as bioburden TYMC (b)(4) mL and Bioburden TAMC (b)(4) mL. The BLA has been amended to correct an error in Section 3.2.S.4.5 to indicate that only the TAMC bioburden test is conducted for the (b)(4) sample.

Satisfactory

S.4.3 Validation of Analytical Procedures

Qualification of the Bioburden (b)(4) Method: drug substance

Qualification of the membrane filtration method was conducted using three batches of formulated drug substance (BDS) in accordance with USP <61> and Eur. Ph. 2.6.12. Summary of bioburden qualification and qualification report RPT_00000223454 - 2.0 is included in section 3.2.S.4.3 of the BLA.

(b)(4)

(b) (4)

(b) (4)

Qualification of the Bioburden (b) (4) Method: (b) (4)

Bioburden method qualification for (b) (4) samples was conducted on three batches in accordance with USP <61> and Eur. Ph. 2.6.12. (b) (4)

(b) (4)

- (b) (4)
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- (b) (4)
- (b) (4)

Acceptance criteria, as described for the BDS qualification, were met.

Qualification of the endotoxin kinetic chromogenic method: drug substance

Suitability of the LAL kinetic chromogenic method was conducted in accordance with USP <85> and EP 2.6.14 for three batches of formulated drug substance.

Qualification report RPT_00000223453 - 1.0 is included in section 3.2.S.4.3 of the BLA.

(b) (4)

(b) (4)

Reviewer's Comment:

The report does not include information regarding preparation of the standard curve or spike level in the (b) (4). Compliance of the endotoxin method qualification with USP <85> was assessed during the pre-license inspection and found adequate.

Satisfactory

Qualification of the endotoxin kinetic chromogenic method: (b) (4) samples. Endotoxin method suitability of (b) (4) samples was conducted in three independent runs of one batch of each (b) (4). Acceptance criteria are as described for the formulated drug substance.

Results of the inhibition and enhancement test for the (b) (4) is summarized in Table 10, modified from Table 2, section 3.2.S.4.3 of the BLA.

Table 10: (b) (4) endotoxin qualification test
(b) (4)

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Additional Studies to support the endotoxin detection method

(b) (4)

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According to the sponsor, the results demonstrate that the method it fit for its intended purpose.

FDA Question 7.a

Indicate how long (b) (4) plates are incubated.

Sponsor's Response in amendment 0012

(b) (4) were incubated (b) (4) days during the bioburden qualification. The plates are incubated (b) (4) days for the routine bioburden test.

Satisfactory

FDA Question 7.b

Justify using the same (b) (4) batch for the three bioburden qualification runs of several of the (b) (4) (b) (4)).

Sponsor's Response in amendment 0012

(b) (4)

Satisfactory

FDA Question 7.c

Repeat (b) (4) endotoxin qualification test using two additional batches.

Sponsor's Response in amendment 0012

The sponsor agrees to repeat the (b) (4) qualification using two additional batches. The qualification is expected to be completed by May

2015; the sponsor response will be updated and the relevant sections of the BLA will be amended.

Sponsor's Response in amendment 0030

Qualification report RPT_00000223458 with data from commercial scale batches PVC0415006 and PVC0115007 is included in the submission. The results show (b) (4) endotoxin recovery of (b) (4)% for the two batches.

Satisfactory

FDA Question 7.d

Endotoxin recovery studies using naturally occurring endotoxin (NOE) isolated from (b) (4) are not representative because they cannot be extrapolated to all other Gram- organisms; endotoxin recovery studies using different NOEs compared side-by-side have shown significant differences depending on the NOE source organism. The studies using CSE show low endotoxin recovery for (b) (4). An alternative endotoxin detection method that does not result in low endotoxin recovery should be explored and developed.

Sponsor's Response in amendment 0012

The sponsor clarifies that the studies in the BLA were not conducted with controlled standard endotoxin (CSE), but with high potency endotoxin. The sponsor is currently conducting studies using reference standard endotoxin (RSE) for mepolizumab drug product and drug substance samples. The studies are expected to be completed by March 2015; the sponsor response will be updated and the section 3.2.S.4.3 of the BLA will be amended. Depending on the results of the study, the sponsor will evaluate further actions for the endotoxin control strategy if required.

Sponsor's Response in amendment 0030

Report RPT_00000322948 using RSE is included in the submission. The report includes endotoxin recovery from (b) (4) (b) (4) spiked with RSE at a target concentration of (b) (4) EU/mL and held for different times (T1 > 25 hours, T2 > 49 hours, and T3 > 8 days). The samples were held on containers representative of manufacturing and sampling containers. (b) (4)

(b) (4)

Satisfactory

S.4.4 Batch Analyses

A summary of the batches manufactured at the different stages of the development and validation of mepolizumab is included in Table 1, section 3.2.S.4.4 of the BLA. The table includes 14 BDS batches from the current process (b)(4) manufactured between November 2012 and June 2014. In addition, 18 commercial scale batches using the (b)(4) process, six (b)(4) batches, and nine (b)(4) batches are also included. Only (b)(4) batches are reviewed here.

The microbial quality results for all batches show (b)(4) (b)(4); endotoxin results are < (b)(4) EU/mg for all for batches, except for T0414005 that shows endotoxin < (b)(4) EU/mg ((b)(4) EU/mg). Batch results include bioburden results for the unprocessed bulk; all results are (b)(4), except batch T0413006 that shows bioburden of (b)(4) (u)(4).

Reviewer's Comment:

Microbial quality for the manufactured batches appears to be acceptable. Batch T0414005 endotoxin result < (b)(4) EU/mg appears to be a typo. Batch T0413006 with unprocessed bulk bioburden of (b)(4) will be review during the pre-license inspection.

FDA Question 8

Clarify if endotoxin release result of batch T0414005 (endotoxin (b)(4) EU/mg) shown in Table 2 of section 3.2.S.4.4 is a typo and amend the table in the BLA.

Sponsor's Response in amendment 0012

The sponsor clarifies that the result was a typo and confirms that the release endotoxin result for batch T0414005 was < (b)(4) EU/mg. The BLA has been amended to show the actual result.

Satisfactory

S.4.5 Justification of Specification

Bioburden Test Specification

Specification bioburden for BDS release is set to (b)(4) (b)(4) The specification was based on manufacturing capabilities; the sponsor considers it adequate for a low bioburden product. The acceptance criterion includes TAMC and TYMC and is (b)(4) (b)(4) mL for both. Specification bioburden for unprocessed bulk is set to (b)(4) (u)(4)

Reviewer's Comment:

(b)(4); therefore, bioburden specifications are appropriate. BDS bioburden testing in stability samples is not required.

FDA Question 9.a

Clarify if a release acceptance criterion is (b)(4)

Sponsor's Response in amendment 0012

The sponsor indicates that acceptance criteria is (b) (4). The BLA has been amended with the revised specifications

Satisfactory

FDA Question 9.b

(b) (4) bulk specification should be changed from (b) (4) CFU/mL to (b) (4) mL.

Sponsor's Response in amendment 0012

The sponsor indicates that the specification of (b) (4) CFU per unit volume should be acceptable; however, the volume increase for the Unprocessed Bulk will be evaluated as indicated in the response to question 2.d.

Satisfactory

Endotoxin Test Specification

Specification limit for BDS release is set to (b) (4) EU/mg based on manufacturing history. The recommended dose for mepolizumab is 100 mg; endotoxin level at the proposed specification would result in (b) (4) EU/dose. Specifications for drug substance and drug product are identical.

Reviewer's Comment:

For a patient with a body weight of 70 Kg; the maximum allowed endotoxin is (b) (4) EU/dose using the USP <85> limit of 5 EU/kg; the specification includes a 17.5-fold safety margin. For an adolescent with a body weight of 40 Kg (50th percentile body weight for a 12 year old boy or girl); the maximum allowed endotoxin is (b) (4) EU/dose using the USP <85> limit of 5 EU/kg; the specification includes a 10-fold safety margin..

Satisfactory

S.6 Container Closure System

The mepolizumab BDS container closure system is a (b) (4) (b) (4). Specifications include sterility of the assembled product (b) (4) and endotoxin (b) (4) EU/mL.

(b) (4)

Reviewer's Comment:

(b) (4) therefore, validation of container closure integrity is not required. Endotoxin specifications per container had been addressed previously for a similar container and were found to be negligible (refer to 125514 microbiology review memo).

During clinical manufacturing campaign in 4Q2013,

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Reviewer's Comment:

The (b) (4) particle issue was discussed during the prelicense inspection. The sterilization of the container closure has been modified to eliminate the risk of (b) (4) in the container.

Satisfactory

S.7 Stability

S.7.1 Stability Summary and Conclusions

The recommended shelf-life of mepolizumab formulated drug substance is (b) (4) months at (b) (4). The stability protocol does not include microbial quality and is not reviewed here.

Reviewer Comments:

Microbial quality results of stability samples are not representative of microbial quality of DS stored in different containers. BDS stability is not required from a microbial quality point of view and is deferred to OBP.

Satisfactory

Environmental Assessment

A categorical exclusion for an action on an application for marketing approval of a biological product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment is claimed under 21 CFR 25.31(c).

cGMP Status

Refer to Panorama for cGMP status of GlaxoSmithKline LLC.

Conclusion

- I. The Drug Substance section of the BLA, as amended, is recommended for approval from a product quality microbiology perspective.
- II. Information and data in this BLA not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. A pre-license inspection was conducted at GlaxoSmithKline LLC. from May 4, 2015 to May 8, 2015 by DMA (Reyes Candau-Chacon), OBP (Marjorie Shapiro and Jennifer Swiffer), and ORA (Gayle Lawson). No 483 was issued. The initial recommendation was NAI. Refer to Panorama for GMP status of the relevant facilities.

FDA Information Request for STN 12555926/0 Microbial Quality – Drug Substance

1. Description of the Manufacturing Process and Process Controls (3.2.S.2.2)

- a.  (b) (4)
- b.
- c.
- d.
- e.
- f.

2. Control of Critical Steps and Intermediates (3.2.S.2.4)

- a.  (b) (4)
- b.
- c.
- d.
- e.

3. Process Validation and/or Evaluation –

- a.  (b) (4)
- b.

**4. Process Validation and/or Evaluation –
Cleaning, Storage, and Reuse**

- a.  (b) (4)

- b. Clarify if the changes between the (b)(4) processes may impact the validation of th (b)(4)

5. Process Validation and/or Evaluation – Shipping Validation (3.2.S.5.3)

- a. Indicate the external temperature during the real time shipping validation study.
- b. Indicate if the location of the data-loggers for the maximum load study during the simulated shipping is the same as indicated in Figure 73 of section 3.2.S.2.5.
- c. Justify not using a minimum load for the real-life shipping validation study.

6. Control of Drug Substance – Analytical Procedures (3.2.S.4.2)

- a. Describe the bioburden and endotoxin methods for DS release, (b)(4) bulk (only bioburden), and (b)(4) samples. Include sample volume, dilution factor if applicable, and bioburden sample incubation conditions.
- b. Clarify if the reported bioburden in the CofA result will be the sum of the TAMC + TYMC and will be specified as such.

7. Control of Drug Substance – Validation of Analytical Procedures (3.2.S.4.3)

- a. Indicate how long (b)(4) plates are incubated.
- b. Justify using the same (b)(4) batch for the three bioburden qualification runs of several of the (b)(4).
- c. Repeat (b)(4) endotoxin qualification test using two additional batches.
- d. Endotoxin recovery studies using naturally occurring endotoxin (NOE) isolated from (b)(4) are not representative because they cannot be extrapolated to all other Gram-organisms; endotoxin recovery studies using different NOEs compared side-by-side have shown significant differences depending on the NOE source organism. The studies using CSE show low endotoxin recovery for (b)(4). An alternative endotoxin detection method that does not result in low endotoxin recovery should be explored and developed.

8. Control of Drug Substance – Batch Analyses (3.2.S.4.4)

Clarify if endotoxin release result of batch T0414005 (endotoxin (b)(4) EU/mg) shown in Table 2 of section 3.2.S.4.4 is a typo and amend the table in the BLA.

9. Control of Drug Substance – Batch Analyses Justification of Specification (3.2.S.4.5)

- a. Clarify if a release acceptance criterion is TAMC (b)(4) (b)(4) mL and TYMC (b)(4) (b)(4) mL or TAMC + TYMC (b)(4) (b)(4) mL.
- b. (b)(4) bulk specification should be changed from (b)(4) to (b)(4) (b)(4) mL.

10. Container Closure System (3.2.S.6)

Manufacture of mepolizumab drug product does not include (b)(4)

FDA Information Request for STN 12555926/0 Microbial Quality – Drug Substance

With regard to your response to question 2.c, the response is not clear. Please provide a diagram showing the bioburden sampling points with respect to th (b) (4)



With regard to your response to question 3.a, based on the growth promotion abilities of the different (b) (4), it is not clear that the (b) (4) is an appropriate surrogate. (b) (4)



With regard to your response to question 5.c, please submit summary results of maximum and minimum load from the simulated shipping studies (IOQ).

FDA Information Request for STN 12555926/0 Microbial Quality – Drug Substance

Indicate the status of the following pending requests and submit the required information to the BLA:

Question 7c, submitted on February 11, 2015: Repeat (b) (4) endotoxin qualification test using two additional batches. Amendment 0012 indicated that qualification of two additional batches of the (b) (4) would be completed by May 2015.

Question 7d, submitted on February 11, 2015 regarding Low Endotoxin Recovery studies. Amendment 0012 indicated that new studies using reference standard endotoxin (RSE) would be completed by March 2015.

Additional request:

Submit endotoxin limits for the (b) (4).

Include bioburden and endotoxin as part of the (b) (4) studies

Maria D.
Candauchacon -S

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ou=FDA, ou=People,
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