

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125526Orig1s000**

**CHEMISTRY REVIEW(S)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Quality

## Quality Team Leader Executive Summary Addendum 2

**From:** Marjorie Shapiro, Ph.D.  
DBRR1

**BLA Number:** 125526  
**Product:** Mepolizumab (Nucala)  
**Sponsor:** GlaxoSmithKline

**Date of Review:** November 4, 2015

## I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

At the time the primary reviews were due, the CMC review team (not including Drug Product microbiology) recommendation was approval; however there were three outstanding issues that required resolution before final approval:

1. **Issues related to the potency assay**
2. **Completion of the DP microbiology review**
3. **Inspectional issues at the DP facility at GSK Parma, Italy resulting in a classification of the inspection as Official Action Indicated**

Items 1 and 2 were previously resolved. The DP micro review was uploaded into Panorama on October 15, 2016. The Quality Team Leader Executive Summary Addendum 1 documents the resolution of items 1 and 2 and activity related to item 3. This memo was uploaded into Panorama on October 20, 2015.

For item 3, a Center Director's Briefing with Dr. Woodcock was held on October 15, 2015, to find a path forward towards approval. The meeting included representatives of DPARP, ODE II, OBP, OPF/DIA, and OC/OMQ. After much discussion, it was determined that OC, with participation from DPARP and OPF/DIA, would schedule a teleconference with GSK to discuss resolution of the outstanding issues and request submission of documentation that demonstrates appropriate remediation of the concerns related to the most serious items in the 483. If upon review by OMQ, the information is determined to be satisfactory, the inspection could be classified as Voluntary Action Indicated, thus allowing a path for approval of the BLA. Otherwise the submitted information would be considered a major amendment and the review clock would be extended.

The teleconference with GSK was held on October 19, 2015 and they submitted their responses to OMQ via email on October 23, 2015. In addition, this document was submitted as an amendment to the BLA.

OMQ initiated a review of the submission and upon review, requested some additional information which was submitted to the BLA on November 3, 2015. This information contains transcription errors and a table and figure related to the sterilization cycle for the stoppers. Upon review of this information, none of the transcription errors were significant in that they impacted the safety, purity or potency of mepolizumab. GSK commits to updating the appropriate sections in the BLA with this information in the first annual report. This is acceptable.

Laura Fontan, the facilities reviewer, prepared an addendum to the primary review describing the inspectional issues at GSK Parma and updated the facilities information in Panorama for both the DS facility in Conshohocken, PA and the DP facility in Parma

SUMMARY BLA125526 Mepolizumab--Nucala

Italy to reflect the VAI status for both. Note that there were no issues raised during the GSK Conshohocken, PA inspection. Her final recommendation states:

"Compliance decisions for the inspection of GlaxoSmithKline LLC drug substance manufacturing facility at Conshohocken, PA (FEI: 3004055938) conducted May 4 to 8th, 2015 and GlaxoSmithKline (GSK) SPA in Torrile, Italy (FEI: 3002807114) conducted from May 19 to 27th, 2015 are complete and acceptable. This application is recommended for approval from a facilities standpoint."

**Note:** The facility is actually in the city Parma Italy with a street address of 43056 San Polo di Torrile.

**IV. SUBMISSIONS REVIEWED**

The table below shows the complete list of CMC amendments submitted and reviewed, including those submitted after October 19, 2015.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 125526/0 (1)	November 7, 2014
STN 125526/12 (13)	March 9, 2015
STN 125526/16 (18)	April 1, 2015
STN 125526/25 (28)	May 14, 2015
STN 125526/30 (31)	June 10, 2015
STN 124426/31 (32)	June 23, 2015
STN 124426/34 (35)	June 29, 2015 follow up to DS micro IRs
STN 124426/38 (39)	July 17, 2015 response to IR #5
STN 124426/40 (41)	July 27, 2015 Bioassay investigation
STN 124426/41 (42)	August 4, 2015 response to LCM requests
STN 124426/47 (48)	September 22, 2015 DP micro
STN 124426/49 (50)	October 4, 2015 DP micro and PMC
STN 124426/52 (54)	October 23, 2015 response to 10/19/15 tcon with OMQ
STN 124426/56 (58)	November 3, 2015 Corrections to Quality Module 3

**VI. SIGNATURE BLOCK (BLA ONLY)**

Name and Title	Signature and Date
Marjorie A. Shapiro, Ph.D. Chief, Lab 1/DBRR1/OBP	<p style="text-align: center;"><b>Marjorie A. Shapiro -S</b></p> <p>Digitally signed by Marjorie A. Shapiro -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S            Date: 2015.11.05 13:59:55 -05'00'</p>

*This review was entered into Pararama on 11/4/15 but due to a system error, it was not signed until 11/5/15*



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51, 10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 11/04/2015  
**To:** Administrative File, STN 125526/0  
**From:** Laura Fontan, Consumer Safety Officer, CDER/OPQ/OPF/DIA  
**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA  
**Subject:** Addendum to Original BLA 125526/0 facility review  
**US License:** 1727  
**Applicant:** GlaxoSmithKline, LLC.  
**Mfg Facility:** Drug Substance: GlaxoSmithKline LLC., 893 River Road, Conshohocken, PA 19428 (FEI: 3004055938)  
Drug Product: GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana 90, 43056 San Polo di Torrile, Parma, Italy (FEI: 3002807114)  
**Product:** Mepolizumab (immunoglobulin G1, anti-IL5) Injection  
**Dosage:** 100 mg/vial lyophilized powder for reconstitution and subcutaneous injection  
**Indication:** Add-on treatment of patients 12 years of age and older with severe eosinophilic asthma as identified by certain blood eosinophil levels  
**Due Date:** 11/04/2015

**RECOMMENDATION:** Compliance decisions for the inspection of GlaxoSmithKline LLC drug substance manufacturing facility at Conshohocken, PA (FEI: 3004055938 ) conducted May 4 to 8<sup>th</sup>, 2015 and GlaxoSmithKline (GSK) SPA in Torrile, Italy (FEI: 3002807114) conducted from May 19 to 27<sup>th</sup>, 2015 are complete and acceptable. This application is recommended for approval from a facilities standpoint.

**Inspection Summary for drug substance site:**

A pre-license and surveillance inspection of GlaxoSmithKline LLC drug substance manufacturing facility at Conshohocken, PA (FEI: 3004055938 ) was conducted May 4 to 8<sup>th</sup>, 2015 . The inspection covered the manufacturing operations for BLA 125526 for mepolizumab drug substance manufacturing at GlaxoSmithKline LLC., as well as general surveillance of the firm. The current inspections were system-based and covered Quality, Facilities and Equipment, Production, Materials, and Laboratory systems. No FDA 483 was issued. However, the following recommendations were made to the firm: (1) to revise the endotoxin limits of the (b) (4) to align it with the endotoxin limits of the (b) (4) (2) to include bioburden and endotoxin (b) (4) (3) to revise the mepolizumab qualification SOP (b) (4) ” to use the acceptance criteria that correspond

to the compendial method, (4) To revisit the sampling strategy of [REDACTED] (b) (4)  
hold times. Recommendations included [REDACTED] (b) (4)

The inspection was classified NAI.

**Inspection Summary for drug product site:**

The inspection of GlaxoSmithKline (GSK) SPA in Torrile, Italy (FEI: 3002807114) a drug manufacturer making [REDACTED] (b) (4) was conducted from May 19 to 27, 2015. The inspection covered the Quality, Facilities & Equipment, Production, and Laboratory Systems as well as profile codes [REDACTED] (b) (4). The current inspection focused [REDACTED] (b) (4) as a Preapproval inspection for BLA125526/0 (Mepolizumab). The inspection resulted in the issuance an 8-item FDA-483, Inspectional Observations including, 1) lack of quality oversight in that documentation was changed specifically for this inspection, 2) complete manufacturing records were not maintained – an operator threw away documentation, 3) failure to establish procedures to prevent microbiological contamination of sterile products, 4) failure to perform adequate cleaning validations for sterile processes, 5) failure to maintain equipment and utensils to prevent contamination for sterile processes, 6) failure of the quality control unit to approve all procedures relating to the test and release of sterile drug products, 7) failure to maintain calibrated equipment within the microbiology laboratory, and 8) failure to maintain appropriate laboratory records.

Additionally, 4 verbal observations were discussed with the firm. These included not maintaining [REDACTED] (b) (4)

Based on the firms response and actions plans, the final classification of this inspection was downgraded from initial OAI to VAI.

Laura  
Fontan -A

Digitally signed by Laura Fontan  
-A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Laura Fontan -A,  
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Date: 2015.11.04 13:51:42 -05'00'

Zhihao  
Qiu -S

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Government, ou=HHS,  
ou=FDA, ou=People,  
cn=Zhihao Qiu -S,  
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Date: 2015.11.04 14:06:16  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Quality

## **Quality Team Leader Executive Summary Addendum 1**

**From: Marjorie Shapiro, Ph.D.  
DBRR1**

**BLA Number: 125526  
Product: Mepolizumab (Nucala)  
Sponsor: GlaxoSmithKline**

**Date of Review: October 15, 2015**

**I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY**

At the time the primary reviews were due, the CMC review team (not including Drug Product microbiology) recommendation was approval; however there were three outstanding issues that required resolution before final approval:

1. **Potency assay:** The potency assay is an IL5 Neutralization Bioassay, (b) (4)

[Redacted]

[Redacted] (b) (4)

In response to a request made during the Late Cycle Meeting, GSK committed to provide batch analysis data for DS and DP batches manufactured during the reporting period to the first BLA annual report. The IL5 neutralization assay is used only for DP release, but is included in DS stability studies.

As also discussed at the Late Cycle Meeting, GSK provided their rationale for including the lower control limit of an ED<sub>50</sub> ratio  $\leq$  (b) (4).



All responses to concerns regarding the IL5 Neutralization Bioassay were adequately addressed.

2. Although Candace Gomez-Broughton, the Drug Product Microbiology reviewer had not identified any concerns that would preclude a recommendation of approval, her review was not completed by July 10, 2015. Subsequent to this, there were additional communications with GSK related to DP micro concerns, as shown in the table below:

Communication/Document	Date
Information Request #5 DP micro	July 9, 2015
Information Request #6 DP micro	September 14, 2015
Teleconference #2 DP micro, including PMC	September 21, 2015
Information Request #7 DP micro	September 30, 2015

The DP microbiology review was finalized and uploaded into Panorama on October 15, 2015. There is one CMC Microbiology PMC (see Section III.). The final DP microbiology recommendation is approval.

3. The inspection of the GSK Parma, Italy facility, which manufactures mepolizumab drug product, was rated as not acceptable and the recommendation of the inspection team was "withhold approval".

Other than concerns with this inspection, there are no outstanding CMC issues from the product quality or microbiology perspectives.

## SUMMARY BLA125526 Mepolizumab--Nucalea

The inspection was a PAI for mepolizumab, as well as a surveillance inspection. The GSK Parma site (b) (4)

(b) (4)

An 8 item 483 was issued with some mepolizumab specific observations. However, these were not the basis for classifying the inspection as potential Official Action Indicated (OAI). The major observations were made in (b) (4)

The observations were related to data integrity issues (making improper changes to a cleaning log book) and raise general GMP concerns that impact the entire facility.

GSK responded to the 483 on June 17, 2015. CDER's Office of Compliance, Office of Manufacturing Quality, Division of Drug Quality 1, was assigned to review the 483, the EIR and GSK's reply to the 483. Based on their review of the Parma inspection and concerns with another GSK site (not related to mepolizumab manufacturing) OMQ agreed with the recommendation of the inspectors to classify the inspection as potential OAI and to issue a warning letter.

This classification would preempt approval of mepolizumab.

Mepolizumab is a first in class product for the treatment of a limited subset of severe asthma patients with significant morbidity and with unmet medical need. Therefore, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) arranged a Center Director's Briefing with Dr. Woodcock to find a path forward towards approval. The meeting included representatives of DPARP, ODE II, OBP, OPF/DIA, and OC/OMQ. After much discussion, OC, with participation from DPARP and OPF/DIA, will call GSK on 10/16/15 and request submission of documentation that demonstrates appropriate remediation of the concerns related to the most serious items in the 483. If upon review by OMQ, the information is satisfactory, the inspection could be classified as Voluntary Action Indicated, thus allowing a path for approval of the BLA.

**I agree with this decision.**

**III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS**

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.

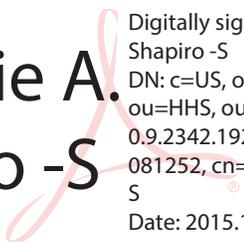
The qualification and implementation of this bioburden test will be submitted as a CBE-0 supplement by June 30, 2016.

**IV. SUBMISSIONS REVIEWED**

The table below shows the complete list of CMC amendments submitted and reviewed, including those submitted after July 10, 2015, including the outcome of the investigation into the shift in results for the IL5 Neutralization Bioassay and responses to DP micro information requests.

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
STN 125526/0 (1)	November 7, 2014
STN 125526/12 (13)	March 9, 2015
STN 125526/16 (18)	April 1, 2015
STN 125526/25 (28)	May 14, 2015
STN 125526/30 (31)	June 10, 2015
STN 124426/31 (32)	June 23, 2015
STN 124426/34 (35)	June 29, 2015 follow up to DS micro IRs
STN 124426/38 (39)	July 17, 2015 response to IR #5
STN 124426/40 (41)	July 27, 2015 Bioassay investigation
STN 124426/41 (42)	August 4, 2015 response to LCM requests
STN 124426/47 (48)	September 22, 2015 DP micro
STN 124426/49 (50)	October 4, 2015 DP micro and PMC

**VI. SIGNATURE BLOCK (BLA ONLY)**

<b>Name and Title</b>	<b>Signature and Date</b>
Marjorie A. Shapiro, Ph.D. Chief, Lab 1/DBRR1/OBP	 <p>Digitally signed by Marjorie A. Shapiro -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S                      Date: 2015.10.20 17:44:16 -04'00'</p>

**First Approval of mepolizumab: for add-on maintenance treatment in patients with severe eosinophilic asthma**

**Recommendation: Approval**

**BLA125526  
Review # 1  
Review Date: July 1, 2015**

<b>Drug Name/Dosage Form</b>	Mepolizumab lyophilate
<b>Strength/Potency</b>	100 mg/vial
<b>Route of Administration</b>	subcutaneous
<b>Rx/OTC Dispensed</b>	Rx
<b>Indication</b>	add-on maintenance treatment in patients with severe eosinophilic asthma
<b>Applicant/Sponsor</b>	GlaxoSmithKline

**Product Overview  
Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Marjorie Shapiro and Jennifer Swisher	Lab 1/DBRR1/OBP Lab1/DBRR4/OBP
Drug Product	Marjorie Shapiro and Jennifer Swisher	Lab 1/DBRR1/OBP Lab1/DBRR4/OBP
Facilities	Laura Fontan	DIA/OPF
Microbiology	Reyes Candau-Chacon (DS) and Candace Gomez-Broughton (DP)	DMA/OPF
Business Regulatory Process Manager	Melinda Bauerlein	DRBPMI/OPRO
Team Lead Microbiology	Patricia Hughes	DMA/OPF
Team Lead Facilities	Peter Qiu	DIA/OPF
Application Technical Lead	Marjorie Shapiro	Lab 1/DBRR1/OBP

**Multidisciplinary Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>OFFICE/DIVISION</b>
RPM	Nina Ton	ODEII/DPARP
Cross-disciplinary Team Lead	Lydia Gilbert McClain	ODEII/DPARP
Medical Officer	Sophia Chaudhry	ODEII/DPARP
Pharm/Tox	Tim Robison	ODEII/DPARP
Clinical Pharmacology	Yunzhao Ren	OCP/DCPII
Statistics	Bob Abugov	OB/DBII

a. Names

- i. Proprietary Name: Nucala
- ii. Trade Name: mepolizumab
- iii. Non-Proprietary/USAN: mepolizumab
- iv. CAS name: 196078-29-2
- v. Common name: none
- vi. INN Name: mepolizumab
- vii. Compendial Name: none
- viii. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P05113 (IL5\_HUMAN) [SB240563]

b. Pharmacologic category: anti-Interleukin 5 monoclonal antibody

Submissions Reviewed:

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
STN 125526/0 (1)	November 7, 2014
STN 125526/12 (13)	March 9, 2015
STN 125526/16 (18)	April 1, 2015
STN 125526/25 (28)	May 14, 2015
STN 125526/30 (31)	June 10, 2015
STN 124426/31 (32)	June 23, 2015

A. Signature Block

<b>Name and Title</b>	<b>Signature and Date</b>
Marjorie A. Shapiro, Ph.D. Primary Product Reviewer and ATL, OBP/DBRRI	 <p>Digitally signed by Marjorie A. Shapiro -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S            Date: 2015.07.16 17:04:54 -04'00'</p>
Kathleen A. Clouse, Ph.D. Director, OBP/DBRRI	 <p>Digitally signed by Kathleen A. Clouse Strebel -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A. Clouse Strebel -S            Date: 2015.07.16 16:57:58 -04'00'</p>

**Quality Review Data Sheet**

**1. LEGAL BASIS FOR SUBMISSION:**

Section 351(a) of the PHS Act

**2. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	2, 3	NA		
	Type III		3	NA			
	Type III		3	NA			
	Type III		2, 3	NA			
	Type III		2, 3	NA			
	Type V		2, 3	NA			

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")

<sup>2</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:** *IND, Reference Listed Drug (RLD), or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 6971	Various amendments	Previous comparability data, PDMS investigation and HCP assay.

(b) (4)

**3. CONSULTS:**

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CMC statistics statistical comparability for DS and DP stability	1/16/15	Complete	Statistical model not adequate	Cassie Dong
CMC statistics small scale manufacturing models	2/5/15	Complete	See below	Cassie Dong

**Note regarding the statistical consults:** The statistical approach was not necessary for DS since the (b) (4) materials are comparable and use the same container closure system. Therefore the (b) (4) long term data can support the shelf life of the (b) (4) process.

Upon receiving a request in IR#3 for additional stability data and a justification that the MDP1 presentation is representative of the MDP2 presentation (b) (4), GSK reconsidered their statistical approach to use MDP1 long term data to support the shelf life of MDP2. They changed their request for the expiration dating period for the commercial MDP2 product to be based on real time data to date on MDP2 lots.

Regarding the small scale studies, the full set of recommendations from Dr. Dong includes:

- Increase the sample sizes used in the qualification studies;
- When the observed variance at the small scale is less than the observed variance at the full scale, we recommend conducting the one-sided F-test to test if the unknown true variance of the small scale is less than the variance at the full-scale.
- We recommend the statistical equivalence testing to assess the equivalence in means.

- We also recommend providing scatter-plots of the individual data for each tested attribute for a side-by-side comparison between the small-scale and the full-scale.
- Provide more information of the multivariate model development, as well as the final fitted models in Process Characterization Studies;
- Provide more information on the Bayesian predictive model development.

However, these studies were performed several years ago and it would be unreasonable to ask the sponsor to perform additional studies now to increase the sample size. The process parameters reported in S.2.2, the validation of the NORs in S.2.5, the PARs determined by the studies described in S.2.6 and the Batch Record controls of the process parameters and in-process controls were compared. Overall, the process parameters in S.2.2 match the PARS in S.2.6. The NORs determined by the validation studies in S.2.5 match the parameters controlled by the Batch Records. In addition, the assessment of quality attributes for the different conditions studied in the small-scale, multivariate and single parameter studies showed that the conditions chosen within the PARS do not alter quality attributes. Therefore, even though several recommendations were made, it was determined that we would not request additional studies or a reevaluation. However, these recommendations were shared with the firm during the BDS PAI for future consideration.

## **Executive Summary**

### **I. Recommendations**

#### **A. Recommendation and Conclusion on Approvability**

##### **a. Recommendation**

The Office of Biotechnology Products, the Division of Microbiology Assessment, Office of Process and Facilities for drug substance microbiology and the Division of Inspectional Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, recommend approval of STN 125526 for Nucala, manufactured by GlaxoSmithKline pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Nucala is well controlled and leads to a product that is pure and potent. We recommend that Nucala be approved for human use under the conditions specified in the package insert.

**Note:** At this time, the compliance checks for all facilities listed, except the mepolizumab drug product manufacturing facility in Parma, Italy, should be acceptable. A substantial 483 was issued for the mepolizumab drug product facility in Parma, Italy. There were mepolizumab specific observations, but these were not considered to be of a nature that would block approval of the BLA. The major observations were made in an area of the facility where mepolizumab is not manufactured; however, these observations raise general GMP concerns that impact the entire facility. It was recommended to classify the inspection as Official Action Indicated (OAI) and the inspection team recommended withholding approval of mepolizumab.

GSK responded to the 483 on June 17, 2015 and at the time this secondary review memo is due to be finalized (July 17, 2015), the Agency decision regarding GSK's response to the 483 is pending.

##### **b. Summary of Complete Response issues**

None

##### **c. Action letter language**

- Manufacturing location:
  - Drug substance – GlaxoSmithKline LLC, Conshohocken, PA 19428
  - Drug product – GlaxoSmithKline Manufacturing S.p.A., Parma, Italy
- Fill size and dosage form – 100 mg/vial
- Dating period:
  - Drug product – 24 months; ≤25°C
  - Drug substance – (b) (4) months; (b) (4) C
- For stability protocols:
  - We approve the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release

- Yes
- Rationale if exempted – specified product
- We exempt specified products according to 601.2a

**d. Benefit/Risk Considerations**

Nucala (mepolizumab) is for the add-on maintenance treatment of patients with severe eosinophilic asthma identified by blood eosinophils  $\geq 150$  cells/ $\mu\text{l}$  at initiation of treatment or  $\geq 300$  cells/ $\mu\text{l}$  in the past 12 months.

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

No CMC Post-Marketing Commitments or Requirements

## II. Summary of Quality Assessments

The control strategy for mepolizumab is based on the identification of critical quality attributes (CQAs), manufacturing and clinical experience, characterization data, analytical method understanding, process understanding, and stability data.

The table in Section A provides a summary of CQA identification and risk management. For the purposes of this table, CQAs are limited to attributes intrinsic to the drug substance (active pharmaceutical ingredient).

The identification and risk management of process related impurities and general drug substance and/or drug product attributes are described in separate risk tables in Section B Drug Substance Quality Summary and Section C Drug Product Quality Summary.

Product variants are defined as variants that are fully active, or close to fully active. Product impurities are defined as product variants that are inactive or have greatly reduced activity.

Overall, GSK took a conservative approach in the identification of CQAs. All quality attributes (QAs) which are “obligatory” or regulatory requirements for quality control were defined as CQAs.

Primary sequence and secondary and tertiary structure were also identified as CQAs. Other QAs were evaluated using a systematic risk assessment. The information for the risk assessment came from clinical, in vivo, in vitro and analytical test data, prior knowledge based on published literature and historical knowledge of other antibodies. Specific for mepolizumab, the biology of the molecule, the mechanism of action, the indication, PK/PD, safety profile, route and frequency of administration and the target population were taken into consideration.



QUALITY REVIEW



A. Mepolizumab CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Aggregate (b) (4) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety  Process	(b) (4)          Minimal increase expected on DS and DP stability.	DS and DP Release testing and stability  SEC-HPLC  Impact on activity is also controlled with the potency assays (SPR for DS and DP and IL5 neutralization assay for DP)	Reduced during (b) (4) step.  CPPs identified for low (b) (4) steps.  Controlled (b) (4) materials
(b) (4) (Product impurity)	Impact on biological activity, immunogenicity, PK/PD, and safety	(b) (4)    Minimal increase expected	DS and DP Release testing and stability  SEC-HPLC and CGE R  Impact on activity is also controlled with the potency assays (SPR for	May be reduced during (b) (4) step.  Controlled (b) (4)



QUALITY REVIEW



		on DS and DP stability.	DS and DP and IL5 neutralization assay for DP)	(b) (4)
(b) (4) (Product variant)	Impact on efficacy and PK/PD	(b) (4) . (b) (4)	Release testing and stability cIEF Impact on activity is controlled with the potency assays (SPR for DS and DP and IL5 neutralization assay for DP)	CPPs identified to control (b) (4) may occur. Controlled via (b) (4)
Antigen Binding (Potency)	MOA - Impact on efficacy	(b) (4)	DS and DP Release testing and stability SPR as a direct measure, Indirect assessment by cIEF, SEC and CGE R + NR as indirect measure	May be reduced during (b) (4)
IL5 Neutralization	MOA - Impact on		DP Release testing and	May be reduced during



QUALITY REVIEW



(Potency)	efficacy	(b) (4)	stability Cell based assay Indirect assessment by SPR, cIEF, SEC and CGE R + NR as indirect measure	(b) (4)
Oxidation (Product variant)	Potential impact on biological activity and PK/PD	Oxidation of (b) (4) (b) (4) (b) (4)	Characterization DS and DP release and stability SPR Indirect assessment by cIEF, SEC and CGE release and stability testing. FcRn binding for characterization	(b) (4)
(b) (4)	Impact on efficacy, safety and immunogenicity	(b) (4)	Not included in control strategy	Characterization and comparability methods Establishment of primary and working RS
	Impact on efficacy,	(b) (4)	Not included in control	Characterization and



(b) (4)

**B. Drug Substance [mepolizumab] Quality Summary: CQA Identification, Risk and Lifecycle Knowledge Management**

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and opalescence (General)	Impact on safety and immunogenicity	(b) (4)	DS release and stability	(b) (4)
Protein Quantity (General)	Impact on efficacy	(b) (4)	DS release and stability	(b) (4)
(b) (4)	Impact on safety and immunogenicity	(b) (4)	(b) (4)	(b) (4)



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				steps/
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	(b) (4)	Data were provided demonstrating that (b) (4) reduced to acceptable levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	(b) (4)	Data were provided demonstrating that (b) (4) s reduced to acceptable levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety	(b) (4)	Data were provided demonstrating that (b) (4) is reduced to acceptable levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety, immunogenicity, and allergenicity	(b) (4)	Data were provided demonstrating that (b) (4) are reduced to acceptable levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety	(b) (4)	Data were provided demonstrating that (b) (4) is reduced to acceptable	(b) (4)



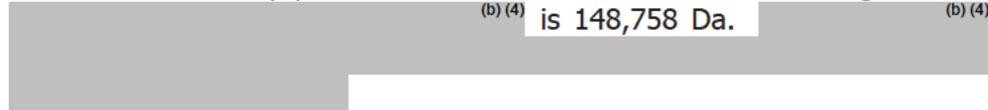
QUALITY REVIEW



			levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety	(b) (4)	Data were provided demonstrating that (b) (4) is reduced to acceptable levels (b) (4).	(b) (4)
(b) (4) (Process Impurity)	Impact on safety		Data were provided demonstrating that (b) (4) is reduced to acceptable levels (b) (4).	
Endotoxin (Contaminant)	Impact on safety	May be introduced at any step	As part of the bioburden control strategy during (b) (4) endotoxin test is part of the (b) (4) testing. Specification at (b) (4) mg	Controlled via (b) (4)
Bioburden (Contaminant)	Impact on safety; product quality due to degradation or modification of product	May be introduced at any step	(b) (4) bioburden test is part of the (b) (4) specifications. Specification at (b) (4) U/10 mL	Controlled via (b) (4)

## a. Description

Mepolizumab (SB240563/Nucala™/MAB HUMANIZED (IGG1) ANTI P05113 (IL5\_HUMAN) [SB240563]) is a humanized IgG1, kappa anti-IL5 monoclonal antibody produced in CHO cells. The molecular weight of the (b) (4) is 148,758 Da. (b) (4)



## b. Mechanism of action

Mepolizumab binds with high affinity to soluble IL5 (b) (4) and blocks IL5 binding to the IL5 $\alpha$  chain of the IL5 receptor on eosinophils and other cells expressing the IL5 receptor. Furthermore, (b) (4) (b) (4) (b) (4) so once mepolizumab is bound to IL5, it stays bound and is not released to become available for binding the receptor. The figure below shows an overlay of the mepolizumab/IL5 complex and the IL5/IL5 $\alpha$  chain complex. Once IL5 is bound to either mepolizumab or the IL5 receptor, steric hindrance prevents binding of the other.



IL5 is a soluble dimer and is not expressed on cell surfaces. Therefore, Fc effector function is not a part of the mepolizumab MOA. In addition, since IL5 cannot bind to both mepolizumab and its receptor at the same time, mepolizumab will not bind to any IL5 already bound to the receptor and therefore, cannot exhibit Fc receptor effector function due to cell surface bound IL5.

## c. Potency Assay

There are two potency assays. The surface plasmon resonance (SPR) assay is used for drug substance release and stability. The IL5 neutralization assay is for DP release and stability and is only used for DS stability.

**SPR:**

(b) (4)

**IL5 Neutralization Bioassay:**

(b) (4)

d. Reference material(s)

(b) (4)

e.

(b) (4)

f.

(b) (4)

(b) (4). The mepolizumab drug substance manufacturing process is well controlled.

g. Container closure

(b) (4)

h. Dating period and storage conditions

The commercial (b) (4) process incorporated minor changes relative to the (b) (4) process. Therefore, the (b) (4) process is considered representative of the commercial process and long term stability data from (b) (4) lots support a commercial expiration dating period. The data support an expiration dating period of (b) (4) months when stored at ≤ (b) (4) C.

### C. Drug Product [Established Name] 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.



QUALITY REVIEW



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

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance (physical state of cake , and color and clarity of reconstituted DP)  (General)	Measure of purity, impact on product safety and immunogenicity	DP manufacture  (b) (4)   	DP Release testing and stability	CPPs identified for lyophilization step.
pH (as reconstituted DP)  (General)	Impact on product stability and conformation	DS manufacture  (b) (4)  	DP Release testing and stability	Controlled (b) (4)  
Osmolality  (General)	Potential impact on therapeutic dose	DS manufacture  (b) (4)  	DP Release testing and stability	Controlled (b) (4)  
Particulate matter (visible and sub- visible)  (General)	Impact on product safety and efficacy	DP manufacture  (b) (4)   	DP Release testing and stability  HIAC	CPPs identified for (b) (4)
Residual Moisture  (General)	Impact on product safety, immunogenicity and therapeutic	DP manufacture  (b) (4)   	DP Release testing and stability	CPPs identified for Lyophilization step



**QUALITY REVIEW**



	dose	(b) (4)		
Reconstitution Time (General)	Impact on product quality	DP manufacture (b) (4)	DP release and stability testing	CPPs identified for Lyophilization step
Weight variation (General)	Impact on efficacy	DP manufacture (b) (4)	DP Weight variation – release testing (b) (4)	CPPs identified for (b) (4)
Protein Quantity (General)	Impact on efficacy	DP manufacture (b) (4)	(b) (4)	CPPs identified for (b) (4)
Endotoxin (Contaminant)	Impact on safety	DP manufacture (b) (4)	Filtration step, (b) (4)	CPPs identified for both steps
Sterility (Contaminant)	Impact on safety	DP manufacture	(b) (4)	CPPs identified for (b) (4)



### QUALITY REVIEW



		(b) (4)	(b) (4)	
			(b) (4)	
Container Closure Integrity (Contaminant)	Impact on safety	DP manufacture (b) (4)	DP Release testing and stability 100% visual inspection and leak test	

a. Potency and Strength

Nucala is supplied as Mepolizumab for Injection, 100 mg/vial drug product, a white lyophilized cake.

b. Summary of Product Design

Nucala is reconstituted with 1.2 mL sterile WFI providing 100 mg of mepolizumab in a 1.0 mL withdrawable volume. The Quality Target Product Profile (QTPP) ensures product quality and safety by the following:

- Product meets and maintains quality attribute targets during manufacture, transport, storage shelf-life and use
- DP does not interact with packaging components to compromise safety and efficacy
- DP that is sterile and with low-endotoxin levels
- Lyophilized DP units to deliver single dose of 100 mg/vial
- Acceptable appearance, essentially free from visible particles after reconstitution
- DP that is suitable for subcutaneous administration and meets pharmacopeial requirements for parenteral administration
- Sufficient shelf life at ≤25 °C to support commercial use

- c. List of Excipients (maximum and minimum values per vial are provided)

Sucrose: (b) (4) mg

Sodium Phosphate Dibasic, Heptahydrate: (b) (4)

Polysorbate 80: (b) (4) mg

(b) (4)

Water for Injection (to (b) (4) mL)

- d. Reference material(s)

Same as for DS

- e. Manufacturing Process

(b) (4)

- f. Container Closure

DP is stored in 10 mL Type 1 clear glass vials, sealed with gray (b) (4) rubber (b) (4) stoppers and aluminum overseals with red flip-off caps.

- g. Expiration Date & Storage Conditions

The shelf life for drug product is 24 months at  $\leq 25^{\circ}\text{C}$ .

- h. List of co-packaged components, if applicable - not applicable

#### D. Novel Approaches/Precedents

The IL5 neutralization assay will be approved with just a lower limit, rather than a range with an upper and lower limit. This is novel for therapeutic mAbs that are not radiolabeled.

The scientific rationale for not having an upper limit includes the extensive knowledge of mepolizumab's MOA, which is that it blocks the interaction between IL5 and its receptor. Furthermore, mepolizumab has high affinity to IL5, which incorporates a slow dissociation constant, suggesting that once bound, IL5 stays bound. Finally, since IL5 is solely a soluble cytokine and crystal structures of IL5 binding to mepolizumab and to the IL5 $\square$  chain show that IL5 cannot bind both at the same time. Therefore, no antibody effector function is involved in the MOA.

In addition to the scientific rationale, the control strategy can detect changes in binding. The SPR method, which has an upper and lower limit, is included as both a release and stability method. Forced degradation studies show that the SPR method is more sensitive than the IL5 neutralization method in detecting changes in binding due to oxidative stress, high and low pH and light exposure. Both methods appear to be equally sensitive to thermal stress.

**E. Any Special Product Quality Labeling Recommendations**

None



QUALITY REVIEW



F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug substance manufacture	(b) (4)  GlaxoSmithKline LLC 893 River Road Conshohocken PA 19428 USA	FEI: 3004055938  DUNS: 929301406	Acceptable	None	Approve



QUALITY REVIEW



<p>Analytical testing of DS and DP</p> <p>Release and stability testing of DS and DP</p> <p>(b) (4)</p>	<p>Biopharmaceutic al Central Testing Laboratories</p> <p>GlaxoSmithKline Medicines Research Centre</p> <p>Gunnels Wood Road</p> <p>Stevenage Hertfordshire</p> <p>SG1 2NY</p> <p>UK</p>	<p>FEI: 3009763376</p> <p>DUNS: 218783633</p>	<p>Inspection waived</p>	<p>NA</p>	<p>Approve based on the facility profile with a reevaluation date of 3/22/2016</p>
<p>(b) (4)</p>	<p>(b) (4)</p>	<p>FEI: (b) (4)</p> <p>DUNS: (b) (4)</p>	<p>Inspection waived</p>	<p>NA</p>	<p>Acceptable</p>



QUALITY REVIEW



	(b) (4)				
(b) (4)		FEI: (b) (4)	Inspection waived	NA	Approve based on the facility profile with a reevaluation date of (b) (4)
manufacture, (b) (4)	GlaxoSmithKline LLC 709 Swedeland Road King of Prussia PA 19406 USA	DUNS: (b) (4)	Not Available	NA	NA
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug product manufacture, primary and secondary	GlaxoSmithKline Manufacturing S.P.A., Strada	FEI: 3002807114 DUNS:	OAI		Pending Compliance Decision



### QUALITY REVIEW



packaging	Provinciale Asolana, 90	338471078			
Release testing of drug product	43056 San Polo di Torrile, Parma, Italy				
Drug product batch release					
Stability testing of drug product					

## G. Facilities

### Prior Inspection History

#### Drug Substance

GlaxoSmithKline (GSK) is British owned with Global headquarters located at 980 Great West Rd., Brentford, Middlesex, TW8 9GS. The GSK Conshohocken, PA site (FEI: 3004055938) has been inspected multiple times since 2003. The most recent inspections are listed below:

- August 19 - 23, 2013 was a pre-license inspection for the manufacture of albiglutide (STN 125431) and was limited to the (b) (4) (b) (4) No Form 483 was issued to the firm. The inspection was classified NAI, however multiple issues were discussed at the close out meeting that require follow up as applicable to Mepolizumab.

- 
- June 7, 2011 was a surveillance inspection which confirmed that (b) (4) was no longer made at the facility and only two investigational drug products were being manufactured; Mepolizumab drug substance (b) (4) (b) (4) and Albiglutide drug substance (b) (4) (b) (4). No commercial product was being manufactured at the time of the inspection. This was the first inspection as GSK and not SmithKline Beecham. The inspection was classified NAI.
  - July 8-10, 2008 was a surveillance inspection which covered the manufacturing operations associated with (b) (4) (b) (4)

(b) (4) In addition, it was confirmed that that the firm was not processing any other pharmaceutical or biological products intended for commercial distribution. Quality and Production Systems were assessed. Although no Form FDA-483 was issued, one deficiency regarding the change frequency of the (b) (4) (b) (4)

(b) (4) was discussed with the firm's management at the conclusion of the inspection. The inspection was classified NAI.

The PAI for mepolizumab DS and cGMP inspection was held between May 4-8, 2015. No 483 was issued.

### Drug Product

GlaxoSmithKline (GSK) is British owned with Global headquarters located at 980 Great West Rd., Brentford, Middlesex, TW8 9GS. The GSK Parma site (FEI: 3002807114) has been inspected multiple times since 2007. The most recent inspections are listed below:

- July 3 - 10, 2013 which covered profile classes (b) (4). Inspection emphasis was centered on sterile manufacturing and controls. The (b) (4) manufacturing areas were covered during inspection. No Form 483 was issued to the firm. The inspection was classified NAI.
- September 17 - 21, 2012 which covered cGMP and PAI for the manufacture of Soriatane (Acitretin) powder filled gelatin capsules (NDA 19821/021) and Trametinib film coated tablets (NDA 204114). No Form 483 was issued to the firm. The inspection was classified NAI. Some conditions were discussed with the firm.
- June 20 -28, 2011 which covered cGMP and PAI for the manufacture of Haloperidol injection (NDA 15923/087) which is manufactured on the GSK Parma ampoule product line (profile class SVS). No Form 483 was issued to the firm. The inspection was classified NAI. Some verbal warnings were discussed with the firm.

The PAI for mepolizumab DP and cGMP inspection was held from May 17-26, 2015. A 483 with 8 observations was issued. The most serious observation was in an area of the facility where mepolizumab is not manufactured. However the concerns are related to general cGMPs and data integrity. The inspection team recommended the inspection be categorized as OAI and recommend withholding approval of the mepolizumab BLA

## H. Lifecycle Knowledge Management

### a. Drug Substance

- i. Protocols approved – Annual GMP stability. No extension of shelf life needed. Protocols for qualification of new working cell banks and reference standards.
- ii. Outstanding review issues/residual risk - None
- iii. Future inspection points to consider – the following recommendation were communicated verbally to GSK during the inspection and should be followed up at the next inspection:
  1. To revise the endotoxin limit of the (b) (4) to align it with the endotoxin limit (b) (4)
  2. To include bioburden and endotoxin in the lifetime studies of (b) (4).
  3. To revise the mepolizumab qualification SOP (b) (4)

(b) (4) to use the acceptance criteria that correspond to the compendial method.

4. (b) (4)

#### b. Drug Product

- i. Protocols approved - Annual GMP stability and extension of shelf life.
- ii. Outstanding review issues/residual risk – Need final report of investigation into shift of values and increased variance reported for the IL5 neutralization assay for MDP2 relative to MDP1 and (b) (4) at BioCTL. The current investigation suggests the shift is not specific to BioCTL and is not due to an inherent change in potency of mepolizumab. (b) (4)

(b) (4). The investigation will be complete by July 31, 2015 and will be submitted to the BLA shortly thereafter. An addendum to the review will be submitted to Panorama upon review of this submission.

- iii. Future inspection points to consider – mepolizumab specific 483 observations
  1. On May 25, 2015, the following were observed within the (b) (4) injectable drugs:
    - Approximately 25, 2-cm circular stains were observed on the ceiling (b) (4)
    - A white residue-like substance was observed (b) (4)
  2. See EIR for other items related to GMP concerns across the facility.

## Quality Assessment Summary Tables

**Table 1: Noteworthy Elements of the Application**

#	Checklist	Yes	No	N/A
<b>Product Type</b>				
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	
<b>Regulatory Considerations</b>				
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 tem)		X	
18.	SPOTS (Special Products On-line Tracking System		X	

19.	USAN Name Assigned		X		
20.	Other _____			X	
<b>Quality Considerations</b>					
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	

**BLA STN 125526**

**Mepolizumab**

**GlaxoSmithKline**

**Marjorie Shapiro, DBRR1/OPB  
Jennifer Swisher, DBRR IV/OBP  
Reyes Candau-Chacon, DMA/OPF  
Patricia Hughes, Acting BC, DMA/OPF  
Laura Fontan DIA/OPF  
Peter Qiu, BC, DIA/OPF**

**ATL Marjorie Shapiro**

OPQ CMC Review Data Sheet

1. **BLA#:** STN 125526
2. **REVIEW DATE:** July, 10, 2015
3. **PRIMARY REVIEW TEAM:**  
**Medical Officer:** Sofia Chaudhry  
**CDTL:** Lydia Gilbert McClain  
**Pharm/Tox:** Tim Robison  
**Product Quality Team:** Marjorie Shapiro, Jennifer Swisher  
**CMC Microbiology:** Reyes Candau-Chacon (DS), Candace Gomez-Broughton (DP), Patricia Hughes  
**Facilities:** Laura Fontan, Christina Capacci-Daniel, Peter Qiu  
**Clinical Pharmacology:** Yunzhao Ren, Satjit Brar  
**Statistics:** Bob Abugov, Greg Levin  
**OBP Labeling:** Jibril Abdus-Samad  
**RPM:** Nina Ton

4. **MAJOR 21<sup>st</sup> Century Review DEADLINES**

Filing Meeting: December 18, 2014  
 Filing Date: January 2, 2015  
 74-Day Letter: January 16, 2015  
 Mid-Cycle Meeting: April 14, 2015  
 Wrap-Up Meeting: September 15, 2015  
 Primary Review Due: July 10, 2015  
 Secondary Review Due: July 17, 2015  
 CDTL Memo Due: September 23, 2015  
 PDUFA Action Date: November 4, 2015

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

Communication/Document	Date
Information Request #1	February 11, 2015
Information Request #2	March 4, 2015
Information Request #3	April, 9, 2015
Information Request #4	June 4, 2015
Teleconference #1	June 24, 2015
Teleconference #1 minutes	June 29, 2015

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

Submission	Date Received	Review Completed (Yes/No)
125526.0 (1)	November 4, 2015	Yes
125526.12 (13) Response to IR #1	March 9, 2015	Yes
125526.16 (18) Response to IR #2	April 1, 2015	Yes

125526.25 (28) Response to IR #3	May 14, 2015	Yes
125526.30 (31) Response to IR #4	June 10, 2015	Yes
125526.31 (32) Response to Telecon Request #1	June 23, 2015	Yes
125526.34 (35) Response to IR #4	June 29, 2015	Yes

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

- a. Proprietary Name: Nucala
- b. Trade Name: mepolizumab
- c. Non-Proprietary/USAN: mepolizumab
- d. CAS name: 196078-29-2
- e. Common name:
- f. INN Name: mepolizumab
- g. Compendial Name:
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P05113 (IL5\_HUMAN) [SB240563]
- i. Other Names: SB-240563, Recombinant humanized monoclonal antibody specific for human IL-5

8. **PHARMACOLOGICAL CATEGORY:** monoclonal antibody

9. **DOSAGE FORM:** lyophilized powder for reconstitution

10. **STRENGTH/POTENCY:** 100 mg/vial

11. **ROUTE OF ADMINISTRATION:** subcutaneous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	(b) (4)	yes	Sufficient leachable and extractable information in BLA. A review of the DMF was performed by Yon-de Lu, PhD, to support NDA (b) (4). The information including the (b) (4) was found to be acceptable
			yes	Sufficient leachable and extractable information in BLA.
			yes	Sufficient leachable and extractable information in BLA.
			yes	Sufficient leachable and extractable information in BLA. A review of the DMF was performed by Ping Jiang-Baucom, PhD, to support

				NDA (b) (4) The information related to the (b) (4) was found to be acceptable.
(b) (4)	yes			Sufficient leachable and extractable information in BLA. A review of the DMF was performed by Kristen Andreson, PhD, to support ANDA (b) (4). The information related to the (b) (4) was found to be acceptable
	yes			Sufficient leachable and extractable information in BLA. A review of the DMF was performed by Jesse Wells, PhD, to support ANDA (b) (4). The information related to the (b) (4) was found to be acceptable.

**13. INSPECTIONAL ACTIVITIES**

The pre-approval inspection (PAI) of the mepolizumab DS and the surveillance inspection for albiglutide at GSK’s facility in Conshohocken, PA was conducted between May 4 -8, 2015. The inspection team consisted of Reyes Candau-Chacon, Jennifer Swisher and Marjorie Shapiro, from CDER/OPQ and Gayle Lawson from ORA, Philadelphia District. No 483 was issued, however 4 recommendations were made by Dr. Candau-Chacon that should be looked into at the next inspection. These include:

1. To revise the endotoxin limit of the (b) (4) to align it with the endotoxin limit of the (b) (4).
2. To include bioburden and endotoxin in the lifetime studies (b) (4).
3. To revise the mepolizumab qualification SOP (b) (4) to use the acceptance criteria that correspond to the compendial method.
4. To revisit the sampling strategy of (b) (4).

The PAI of the mepolizumab DP at GSK’s facility in Parma, Italy was conducted between May 18 – 26, 2015. The review team consisted of Laura Fontan, OPQ/OPF, April Young, ORA, Minneapolis District, and Diane Riccasi, ORA, headquarters. A 483

with 8 observations was issued. Four observations are related to the same concern regarding (b) (4)

The 5 observation is related to poor maintenance of equipment and utensils. Specific to mepolizumab

- Approximately 25, 2-cm circular stains were observed on the ceiling directly above the (b) (4) for Mepolizumab lot 5002.
- A white residue-like substance was observed on the partition directly above the (b) (4) for Mepolizumab lot 5002

Observations 6 and 7 are related to the (b) (4) endotoxin testing in the (b) (4) and observation 8 is related to incomplete information in a log book for a pH meter in the microbiology lab.

The data integrity concerns related to the first 4 observations need to be satisfactorily addressed prior to approval of the BLA.

The inspection of GSK’s testing site, BioCTL, in Stevenage, UK was waived because it had been inspected within the past two years.

**14. CONSULTS REQUESTED BY OBP**

CMC statistics: 1/16/2015 Xiaoyu (Cassie) Dong for analysis of DS and DP stability data and 2/5/15 for analysis of small-scale models used to support PARs. Both consult reviews were completed by 4/10/15.

**15. QUALITY BY DESIGN ELEMENTS**

The following was submitted in the identification of QbD elements (check all that apply):

no	Design Space
yes	Design of Experiments
yes	Formal Risk Assessment / Risk Management
yes	Multivariate Statistical Process Control
no	Process Analytical Technology
no	Expanded Change Protocol

**16. PRECEDENTS**

The IL5 neutralization assay is approved with just a lower limit, rather than a range with an upper and lower limit. This is novel for therapeutic mAbs that are not radiolabeled.

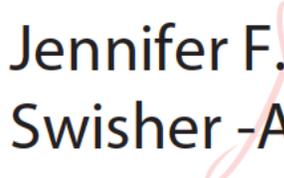
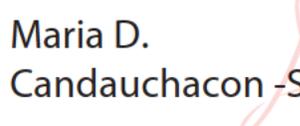
The scientific rationale for not having an upper limit includes the extensive knowledge of mepolizumab’s MOA, which is that it blocks the interaction between IL5 and its receptor. Furthermore, mepolizumab has high affinity to IL5, which incorporates a slow dissociation constant, suggesting that once bound, IL5 stays bound. Finally, since IL5 is

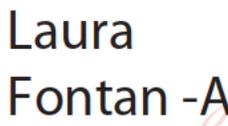
solely a soluble cytokine and crystal structures of IL5 binding to mepolizumab and to the IL5 $\alpha$  chain show that IL5 cannot bind both at the same time. Therefore, no antibody effector function is involved in the MOA.

In addition to the scientific rationale, the control strategy can detect changes in binding. The SPR method, which has an upper and lower limit, is included as both a release and stability method. Forced degradation studies show that the SPR method is more sensitive than the IL5 neutralization method in detecting changes in binding due to oxidative stress, high and low pH and light exposure. Both methods appear to be equally sensitive to thermal stress.

**17. ADMINISTRATIVE**

**A. Signature Block**

Name and Title	Signature and Date
<p>Marjorie A. Shapiro, Ph.D. Primary Product Reviewer and ATL, OBP/DBRRI</p>	 <p>Digitally signed by Marjorie A. Shapiro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S Date: 2015.07.09 14:08:33 -04'00'</p>
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<p>Kathleen A. Clouse, Ph.D. Director, OBP/DBRRI</p>	 <p>Digitally signed by Kathleen A. Clouse Strebel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A. Clouse Strebel -S Date: 2015.07.09 12:06:42 -04'00'</p>
<p>Reyes Candau-Chacon, Ph.D Primary DS Microbiology Reviewer, OPF/DMA</p>	 <p>Digitally signed by Maria D. Candauchacon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S Date: 2015.07.09 13:12:45 -04'00'</p>

<p>Colleen Thomas, Ph.D., for Patricia Hughes, Ph.D. Acting Branch Chief, OPF/DMA</p>	 <p>Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334597 Date: 2015.07.09 13:25:59 -04'00'</p>
<p>Laura Fontan, Ph.D. Primary Facility Reviewer, OPF/DIA</p>	 <p>Digitally signed by Laura Fontan -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laura Fontan -A, 0.9.2342.19200300.100.1.1=2001525652 Date: 2015.07.09 14:01:40 -04'00'</p>
<p>Steven Fong, Ph.D., for Peter Qiu, Ph.D. Branch Chief, OPF/DIA</p>	 <p>Digitally signed by Steven Fong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Fong -S, 0.9.2342.19200300.100.1.1=2000287433 Date: 2015.07.09 12:55:56 -04'00'</p>

**B. CC Block**

Phuong Nina Ton, RPM DPARP	Provided Electronically
Lydia Gilbert McLain, MD, CDTL DPARP	Provided Electronically

**SUMMARY OF QUALITY ASSESSMENTS**

**I. Primary Reviewer Summary Recommendation**

The Office of Biotech Products, DIA/OPF and DMA/OPF for drug substance, OPQ, CDER recommend approval of STN 125526 for Nucala™ manufactured by GlaxoSmithKline LLC, pending acceptable compliance checks. The data submitted in the BLA support the conclusion that the manufacture of Nucala™ (mepolizumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and infectious adventitious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing are sufficiently validated and a consistent product has been manufactured from multiple production runs. It is recommended that Nucala™ (mepolizumab) be approved for human use under conditions specified in the package insert.

We recommend an expiration dating period of <sup>(b)(4)</sup> months for mepolizumab drug substance when stored at <sup>(b)(4)</sup> °C.

We recommend an expiration dating period of 24 months for mepolizumab drug product (100 mg/vial) when stored at ≤25°C ±2% RH.

We recommend approval of the proposed release and shelf life specifications for mepolizumab drug substance and drug product.

There is one outstanding review issue at the time the primary review is due under GRMPs. GSK is completing an investigation into an apparent shift in the results of the IL5 neutralization assay upon transfer to BioCTL, the commercial QC release and stability testing site. However this is only seen for MDP2 lots and not (b)(4) lots. The likely reason is due to (b)(4). This was discussed during a teleconference on June 24, 2015. GSK will submit the results of the final investigation, which is due to be completed on July 31, 2015. An addendum to the primary review will be submitted upon review of the final investigation. There should be sufficient time for GSK to submit the investigation for review prior to any final action by the PDUFA deadline, November 4, 2015.

The DMA/OPS drug product review and recommendation will be contained in a separate document.

II. List Of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirement: None

IV. Review Of Common Technical Document-Quality Module 1

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

A separate primary container labeling review will be performed by Jibril Abdus Samad and reviewed by Marjorie Shapiro

VI. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The anti-drug antibody immunogenicity assay has sufficient sensitivity (1.03 ng/ml) and demonstrates sufficient drug tolerance (detects 250 ng/mL ADA in the presence of up to 100 µg/ml mepolizumab). The current neutralizing antibody assay is a cell-based assay that possesses lower, but sufficient sensitivity (600 ng/ml) and demonstrates a lower degree of drug tolerance (detects 3.5 µg/ml in the presence of up to 1 µg/ml mepolizumab). Due to the low rate of immunogenicity, the effect of ADA seen on mepolizumab PK, and the ability of the assay to detect neutralizing antibodies after a washout period, the neutralizing assay is acceptable.

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(b) (4)



### **3.2.S.4 Control of Drug Substance (MAS, JFS and RCC)**

#### **3.2.S.4.1 and 3.2.S.4.5 Specification and Justification of Specification (MAS and RCC)**

The proposed commercial specifications were derived using a statistical approach to analyze release and stability (End of Shelf Life EOSL) data from (b) (4) materials. Figure 1 (not copied in review) depicts the steps in graphical form. In brief:

(b) (4)



DP data are reviewed in detail in P.5.6. For DS, the EOSL data showed no degradation during DP manufacture, (b) (4). For DS release different approaches were used depending on whether degradation was observed on stability:

- For methods where there was no degradation on stability, release acceptance criteria are the same as for EOSL.

(b) (4)



**Table 1 Specification for Mepolizumab Drug Substance**

Test	Method	Acceptance Criteria For Release and Shelf Life Unless Noted as Different
<b>Appearance</b>		
Appearance	Visual Observation Ph.Eur. 2.2.1, 2.2.2	(b) (4)
<b>General Tests</b>		
pH	USP <791> Ph.Eur. 2.2.3	(b) (4)
<b>Quantity</b>		
Protein Concentration	Variable Pathlength UV/VIS	(b) (4) mg/mL
<b>Identity</b>		
Surface Plasmon Resonance (SPR)	IL5 Binding Assay	Identity confirmed
Capillary Isoelectric Focusing (cIEF)	Capillary Electrophoresis	Comparable to reference standard
<b>Purity</b>		
Size Exclusion Chromatography (SEC)	Size Exclusion Chromatography	(b) (4) (b) (4) % (b) (4) (b) (4) %
Reduced Capillary Gel Electrophoresis (CGE)	Capillary Gel Electrophoresis	% Purity ≥ (b) (4) %
Capillary Isoelectric Focusing (cIEF)	Capillary Electrophoresis	Comparable to Reference Standard % Main Peak ≥ (b) (4) % % Total Acidic ≤ (b) (4) %
<b>Potency</b>		
Surface Plasmon Resonance (SPR)	IL-5 Binding Assay	Specific Binding Activity (b) (4)
<b>Impurities</b>		
(b) (4)		Release: ≤ (b) (4) ng/mg
<b>Safety</b>		
Endotoxin	USP <85> Ph.Eur 2.6.14	Release: ≤ (b) (4) EU/mg
Bioburden	USP <61> Ph. Eur. 2.6.12	Release: ≤ (b) (4) mL
(b) (4)		
Bioburden	USP <61>, Ph. Eur. 2.6.12	Release: ≤ (b) (4) mL
Mycoplasma	USP <63>, Ph. Eur. 2.6.7	Release: Not Detected
In vitro adventitious agents	Combined Test Using (b) (4) (b) (4) Cell Lines	Release: Not Detected

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**3.2.S.7.3 Stability Data**

**Reviewer comment (MAS):** This section contains tables containing all the stability data for pilot, (b) (4) lots stored at all conditions. The data are summarized above, but all the data tables were reviewed.

**P DRUG PRODUCT [Mepolizumab for Injection, 100 mg/vial]**

**3.2.P.1 Description and Composition of the Drug Product (MAS)**

Mepolizumab for Injection, 100 mg/vial, drug product (DP) is a white lyophilized cake, containing (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. It is reconstituted with 1.2 mL of sterile Water for Injection (WFI) and forms a clear-to-opalescent, colorless to pale-yellow or pale-brown solution that is essentially particle-free. Administration is sub-cutaneous

**Table 1 Composition of Mepolizumab for Injection, 100 mg/vial**

Component	Quantity per vial <sup>1</sup> (mg)	Function	Quality Standards
Mepolizumab	(b) (4)	Drug Substance	GSK, Non-compendial
Sucrose	(b) (4)	(b) (4)	USP/NF, EP, and JP
Sodium Phosphate Dibasic,	(b) (4)	(b) (4)	USP
Polysorbate 80	(b) (4)	(b) (4)	USP/NF, EP, and JP
(b) (4)	(b) (4)	(b) (4)	USP/NF, EP, and JP
Water for Injection <sup>2</sup>	(b) (4)	(b) (4)	USP/NF, EP, and JP

- Minimum and maximum values per vial are provided for excipients.
- The product contains (b) (4) mg/vial; the label claim of 100 mg/vial (b) (4) overfill allows a withdrawal volume of 1.0 mL after reconstitution with 1.2 mL of SWFI. (b) (4) results in a final concentration of 100mg/mL. No overages are included.
- (b) (4)

**3.2.P.2 Pharmaceutical Development (MAS)**

**3.2.P.2.1 Components of the Drug Product (MAS)**

Three lyophilized Mepolizumab for Injection presentations have been used throughout clinical development that have different amounts of mepolizumab per vial: 50 mg/vial for early clinical studies; 250 mg/vial for Phase 2 and the beginning of Phase 3 or other late phase clinical studies; and 100 mg/vial was introduced in 3Q2013 for ongoing clinical studies including two open label studies for asthma. The 100 mg/vial is the proposed commercial DP. The quality target product profile (QTPP) is:

- Product meets and maintains quality attribute targets during manufacture, transport, storage shelf-life and use
- DP does not interact with packaging components to compromise safety and efficacy
- DP that is sterile and with low-endotoxin levels

- Lyophilized DP units to deliver single dose of 100 mg/vial
- Acceptable appearance, essentially free from visible particles after reconstitution
- DP that is suitable for subcutaneous administration and meets pharmacopeial requirements for parenteral administration
- Sufficient shelf life at  $\leq 25$  °C to support commercial use

Attributes of BDS required for the DP to meet the QTPP include:

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]
- [Redacted]

The decision to develop a lyophilized DP [Redacted] (b) (4)

**Reviewer comment (MAS):** Note that [Redacted] (b) (4)

Table 1 (not copied in review) shows the DP quality attributes assessed throughout clinical development include appearance, color clarity, identity, protein quantity, [Redacted] (b) (4), [Redacted] (b) (4), pH, osmolality, reconstitution time, residual moisture, polysorbate 80 concentration, particulates, oxidation [Redacted] (b) (4) variants, [Redacted] (b) (4), phase identification of [Redacted] (b) (4), volatile and semi-volatile extractables and [Redacted] (b) (4). The table also shows the methods used to assess these attributes throughout clinical development. Methods that changed between Phases 1 and 2 and the Phase 3 and commercial lots include those for [Redacted] (b) (4)

The formulation components did not change throughout the course of development, but quantitative changes [Redacted] (b) (4) were made that led to [Redacted] (b) (4) (Table 2).

**Table 2 BDS Formulations for DP Manufacture to Support Pre-Clinical, Clinical Studies, and Commercialization**

Component	Pre-Clinical Formulation	Phase I Formulation	Phase IIa, <sup>7</sup> IIb, III, and Commercial Formulation	Quality Standard	Function
Mepolizumab (mg/mL)	(b) (4)	(b) (4)	(b) (4)	Non-Compendial <sup>1</sup>	Active ingredient
Sucrose (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP/NF <sup>2</sup> , EP <sup>3</sup> , and JP <sup>4</sup>	(b) (4)
Sodium phosphate dibasic, heptahydrate (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP <sup>5</sup>	(b) (4)
PS80 (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP/NF, EP, and JP	(b) (4)
Water for Injection (WFI)	(b) (4)	(b) (4)	(b) (4)	USP/NF, EP, and JP	(b) (4)

**Reviewer comment:** The remainder of this section describes studies performed to aid in the selection of the formulation pH and (b) (4) composition. These studies include the effect of pH on mepolizumab solubility and stability when exposed to different temperatures and light; the effect of ionic strength on solubility; the optimum sugar (sucrose), concentration and (b) (4) at different temperatures and exposure to light (b) (4); and the (b) (4) PS80 concentration to (b) (4). Sufficient details are provided that justify the final choice of the formulation.

**Effect of light exposure during BDS and DP manufacturing:** Three lots of BDS (b) (4) process lot 240563-0XB0-C03 and MDS I lots T04H001, and T04H004) were tested per ICH Q1B for photostability. The formulation of these BDS lots is the same as the 100 mg/vial, so the results are applicable to DP. Each of the three lots showed an increase (b) (4) and a decrease in IL5 binding upon exposure to light.

To assess the exposure to light during DP manufacturing (b) (4) samples were placed in the same type of (b) (4) used during DP manufacture, which represents the highest exposure to (b) (4). Samples were assessed for (b) (4) appearance, pH, and protein quantity after 14 hours of light exposure. All attributes met acceptance criteria and no changes were detected in appearance, pH or protein quantity. There were slight changes in the other attributes (Table 9, not copied in review) that suggest (b) (4) are most likely to be affected by light exposure.

**Reviewer comment (MAS):** Overall, these studies support that the BDS formulation ( (b) (4) mepolizumab, (b) (4) sodium phosphate dibasic heptahydrate, (b) (4) sucrose, (b) (4) PS80, pH 7.0) meets requirements for DP to meet the QTPP.

### 3.2.P.2.2 Drug Product (MAS)

**Reviewer comment (MAS):** Some of the information in this section is redundant with information in P.2.1. Other information provides additional details of studies to support excipient selection for the sucrose, polysorbate 80 and mepolizumab concentrations and focused on attributes (b) (4). Only the final study (Study 4) is described, since it confirmed the final formulation using the most current analytical methods.

Table 1 (not copied in review) shows the DP composition (mg/vial of each component). Tables 2 and 3 (not copied in review) show the genealogy of the DS and DP batches and formulations of each batch used for pre-clinical, clinical and stability studies. Table 4, not copied in review summarizes the excipient selection and optimization studies. These studies focused on (b) (4) selection (sucrose (b) (4) polysorbate 80 concentration, pH and mepolizumab concentration.

Study 4: The purpose of this study was to confirm the formulation for the 100 mg vials. Updated methods (SPR, cIEF, CGE and variable pathlength UV/VIS) replaced the older methods used at the time of the earlier studies. Lyophilized DP was stored for 3 months at 5°C or 40°C/75% RH. Samples were tested for (b) (4), osmolality, general appearance, protein concentration, pH, IL-5 binding activity, (b) (4) and sub-visible particles. The different formulations had no effect on general appearance, protein concentration, pH, IL-5 binding activity, (b) (4) and sub-visible particles or for (b) (4) at 5°C (Figures 12 and 14, not copied in review). (b) (4)

**Reviewer comment (MAS):** This study confirms the choice of (b) (4) sucrose and (b) (4) PS80 for the commercial formulation. Together, studies 1-4 support the ability of the chosen formulation to meet the QTPP and provide and acceptable (b) (4)

**Figure 16** (b) (4): Effect of (b) (4) Sucrose Concentrations on Reconstituted Mepolizumab for Injection DP



**Stability of Mepolizumab for Injection 100 mg/vial:** Previous studies showed that mepolizumab is sensitive to light, but lyophilized DP (250 mg/vial presentation) is relatively insensitive to light exposure. A photostability study was performed on Mepolizumab for Injection 100 mg/vial to determine if the commercial product has the same sensitivity to light as the 250 mg/vial clinical product. DP batch 3501 ((b) (4)) was used for the study and tested for identity, purity and potency (release testing). Samples were tested at the beginning of the study and light exposed samples were compared to control samples. All acceptance criteria were met (Table 5, not copied in review), but there were slight decreases in purity by SEC (b) (4) and cIEF (b) (4)).

**Reviewer comment (MAS):** This study confirms that lyophilized mepolizumab DP in the commercial presentation is relatively insensitive to light exposure. Details of the study are contained in P.8.3.

**Overages:** There are no overages in the Mepolizumab for Injection 100 mg/vial. There is an overfill of (b) (4) per vial since the entire reconstituted volume is not recoverable. Upon reconstitution with 1.2 mL WFI, the final volume is (b) (4) at a concentration of 100 mg mepolizumab/mL. The label claim of 100 mg/mL is based on a withdrawable volume of 1.0 mL.

**Sub-Visible Particle Characterization:** The release method (HIAC) and microflow imaging (MFI) were used to characterize sub-visible particles (SVP)  $\geq$  (b) (4)  $\mu\text{m}$  and MFI was also used to characterize (b) (4)  $\mu\text{m}$  particles. Particles  $\leq$  (b) (4)  $\mu\text{m}$  include (b) (4) and are monitored by SEC. Currently, there are no adequate technologies to monitor (b) (4)  $\mu\text{m}$  SVP.

**HIAC** – Light obscuration HIAC quantifies SVP, but cannot differentiate the types of particles. A small volume HIAC method comparable to the USP 788 HIAC method was used during development with the acceptance criteria of  $\leq$  (b) (4) particles  $\geq$  (b) (4)  $\mu\text{m}$  and  $\leq$  (b) (4) particles  $\geq$  (b) (4)  $\mu\text{m}$  per container.

**MFI** – MFI can quantify particles and evaluate the morphology of particles. One advantage over other methods is that it can detect translucent particles, which are often proteinaceous. Samples stored for 18 months at 25°C/60% RH were used to analyze particle morphology using the aspect ratio parameter (ratio of a particle's minor axis length over the major axis length). An aspect ratio of  $>$  (b) (4) represents round particles, which could be silicone oil droplets or air bubbles (Figure 17, not copied in review). Particles with an aspect ratio  $\leq$  (b) (4) are not round and are typically proteinaceous (Figure 18, not copied in review).

**HIAC vs MFI Comparison:** DP 250 mg/vial batches 0001, 1001, and 2003 were stored at 5°C or 25°C/60% RH for 18 months and analyzed by both methods at 0, 6, 9, 12 and 18 months.

**SVP** (b) (4)  $\mu\text{m}$  - HIAC showed no increase over time among the three lots when stored at either temperature (Figures 18 and 20, not copied in review). The number of SVP ranged from  $<$  (b) (4). HIAC also showed no increase over time among the three lots when stored at either temperature (Figures 21 and 22, not copied in review). The number of SVP ranged from (b) (4).

**SVP** (b) (4)  $\mu\text{m}$  – Similar observations were made by both methods for SVP  $\geq$  (b) (4)  $\mu\text{m}$  in that there were no increases over time at either storage conditions (Tables 6 -9, not copied in review). The  $\geq$  (b) (4)  $\mu\text{m}$  particles ranged from (b) (4) and the  $\geq$  (b) (4)  $\mu\text{m}$  particles ranged from (b) (4) by HIAC. For MFI, the  $\geq$  (b) (4)  $\mu\text{m}$  particles ranged from (b) (4) (with one outlier at (b) (4) at T6 months) and the  $\geq$  (b) (4)  $\mu\text{m}$  particles ranged from (b) (4).

**Reviewer comment (MAS):** Since MFI is more sensitive than HIAC, it is expected that the particle count would be higher by this method. The number of proteinaceous particles determined by MFI were not provided, but overall the results from both methods were consistent and even the MFI results met the USP criteria, with the one outlier for  $\geq$  (b) (4)  $\mu\text{m}$  particles. GSK states that SVP (b) (4)  $\mu\text{m}$  particles will be quantitated by HIAC as part of the GMP stability program for information only. Future commercial lots will not be analyzed by MFI. This is acceptable.

### 3.2.P.2.3 Manufacturing Process Development (MAS)

#### 3.2.P.2.3.1 Overview

(b) (4)

### **3.2.P.2.4 Container Closure System (MAS)**

#### **4.1 Introduction**

Table 1 provides the components of the container closure system and their suppliers.

**Table 1 DP Container Closure System Configuration**

Component	Description	Manufacturer
Vial	10-mL, Type 1 glass vial	(b) (4)
Stopper	(b) (4) gray, (b) (4) rubber (b) (4) stopper	(b) (4)
Overseal <sup>1</sup>	(b) (4) overseal with a matte, red plastic flip-off cap	(b) (4)

**4.2 Primary Packaging**

Table 2 (not copied in review) shows a comparison between the container closure systems used during early clinical studies and the Phase III and commercial process. Although the materials have not changed, (b) (4)

Stability studies at long term, accelerated, stress, and freeze-thaw conditions were used to assess the suitability of the container closure system.

Data regarding moisture permeation, light exposure and microbial contamination are found in P.8.3 Stability Data. However, studies support the use of the container closure system regarding these parameters.

Container closure integrity was also validated using (b) (4) (see P.3.5 Process Validation)

See P.6 Container Closure for additional details regarding the composition of the components and letters of authorization for the components.

**4.3 Extractables and Leachables**

DP stored for 12 months at 25°C/60% RH had no leachables detected at a level that would be a risk to patient safety. Studies of vials stored at 40°C/75% RH showed that the potential exposure to leachables through the proposed shelf life is low.

**3.1 Introduction:** A 3-step approach was used to evaluate leachables:

1. A formal risk assessment was conducted for potential manufacturing process (BDS and DP) and container closures system (BDS and DP) failure modes that could lead to patient exposure to leachables. The risk assessment was performed using a FMEA to identify materials that have a higher chance of leaching.
2. Once a risk was identified, extractable studies were conducted. These studies have provided information used for leachable method development; or when worst-case extraction conditions and (b) (4) were used, they provided an insight into potential leachables.
3. Leachable studies were conducted to better establish the type and quantity of leachables present in DP. Specific leachable methods were developed based on the results of the extractable studies. Safety assessments were performed on leachables that were identified

as being above the pre-established threshold limits set in the leachable studies. This threshold was also applied to the extractable studies.



(b) (4)

**Risk Assessment of the BDS Manufacturing Process and Container Closure System:**

(b) (4)

. Table 3 provides the BDS failure modes that were investigated.

**Reviewer comment (MAS):** GSK states that

(b) (4)

I agree with this assessment.

**Risk Assessment of the DP Manufacturing Process and Container Closure System:** Table 4 provides the DP failure modes that were investigated.

For (b) (4) DP, the container closure leachables are considered to be higher risk than manufacturing process leachables, due to time of contact with the materials.

**3.3 Definition of the Threshold Limit for the Analytical Evaluation of Extractables and Leachables in Mepolizumab DP:** Since there are no specific guidelines for leachables in parenteral DPs, defined in the EMEA guidance on Limits of Genotoxic impurities and ICH M7 on Mutagenic impurities were used to establish the threshold for toxicological concern.

The threshold for detection, identification, and quantitation of leachables was set at (b) (4)  $\mu\text{g}$  per day for a lifetime of daily exposure. The analytical methods used in these studies were sufficiently sensitive to detect these levels. Therefore, any individual leachable present at levels equivalent to a daily intake of (b) (4)  $\mu\text{g}/\text{day}$  would be considered a negligible safety concern and was not included in experimental studies.

**Table 3 BDS: Failure Modes Warranting Further Investigation**

Route of Exposure	Failure Mode	Stage
(b) (4)		

Mepolizumab is administered once every 4 weeks with a maximum dose of 100 mg. DP is reconstituted in 1.2 mL WFI and 1.0 mL is given to patients. Therefore, the threshold of detection for leachables from the container closure is (b) (4)  $\mu\text{g}$  per 100 mg dose, which is equivalent to (b) (4)  $\mu\text{g}/\text{day}$ .

**3.4 BDS Studies:** Data for the (b) (4)

(b) (4)

(b) (4)

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(b) (4)

**Reviewer comment (MAS):** Overall, there does not appear to be a risk to patient safety from BDS process or container leachables.

(b) (4)

**3.7 DP Container Closure System Extractable & Leachable Studies:** Both the Type 1 glass vial and the <sup>(b) (4)</sup> rubber stopper have direct contact with DP. For the glass vials, extraction studies were conducted to evaluate metal species. Since glass vials are considered to be inert, more comprehensive studies were not considered necessary.

Extractable studies evaluated volatiles, semi-volatiles, antioxidants, fatty acids, metal species, and <sup>(b) (4)</sup> associated with the rubber stoppers using analytical techniques such as GC, HPLC, and ICP. The aim of the leachable studies was to identify leachables and determine the effect of storage time and temperature on the levels of leachables in DP. Vials from three batches were stored inverted at 25°C/60% RH and will be tested regularly for up to 60 months and additionally at 40°C/75% RH for up to 12 months. These are considered worst-case conditions for leachates.

These studies include:

- <sup>(b) (4)</sup>
- <sup>(b) (4)</sup>
- <sup>(b) (4)</sup>

(b) (4)

(b) (4)

overall exposure levels indicate that the DP container closure presents a negligible risk of patient exposure to leachables.

### 3.2.P.2.5 Microbiological Attributes

**Reviewer comment (MAS):** Deferred to DMA/OPF

### 3.2.P.2.6 Compatibility (MAS)

**6.1 Overview:** Compatibility of reconstituted DP with glass vials and polypropylene (PP) syringes was assessed by stability studies that mimic reconstitution, administration, and short-term storage.

**6.2 Compatibility of Reconstituted Solution in Glass Vials:** The reconstituted vials were stored either protected from or exposed to ambient light (approximately 1200 Lux) at temperatures ranging from 5°C to 30°C for 4 hours and 8 hours and compared to freshly reconstituted DP. Samples were tested for general appearance, pH, protein quantity, SEC, CGE, IL-5 binding, cIEF, particulate matter, and peptide mapping. Table 1 (not copied in review) shows that all samples, protected from and exposed to light, at both temperatures and at 4 and 8 hours met acceptance criteria. Overall the reconstituted solution is biochemically stable for up to 8 hours up to 30°C. Unused reconstituted solution should be discarded after 8 hours.

**Reviewer comment (MAS):** The results demonstrate compatibility of DP with the vials during the course of normal administration. There were some minor trends seen at the elevated temperature of 30°C; there was an increase (b) (4) in samples exposed to light at 4 and 8 hours ((b) (4)%) and there was an increase in particulate matter between (b) (4) mm for all samples, with slightly higher levels in light exposed vials. (b) (4)

**6.3 Stability after Reconstitution using a Swirling Device:** An IKA Vortex 4 digital swirling device with universal attachment and test tube foam insert at various rpm settings was used to aid reconstitution. Three swirling conditions were tested: 300 rpm for 15 minutes; 450 rpm for 10 minutes; and 1000 rpm for 5 minutes. Four vials were tested at each condition. Prior to vortexing, vials were manually swirled for 30 seconds to wet the lyophilized cake evenly. A manually reconstituted vial was the control. Reconstituted DP was assessed for general appearance; potency by SPR; CGE, SEC, and cIEF; protein concentration; pH; reconstitution time; and particulate matter by HIAC. Table 2 (not copied in review), shows that all samples for each swirling condition met the criteria.

**Reviewer comment (MAS):** The results were consistent among the conditions with no apparent trends within the quality targets.

**6.4 Stability and Compatibility with Syringes used for Administration:** The stability of DP at 100 mg/ml in a PP syringe with a 23G stainless steel needle was tested by storing filled syringes either protected from or exposed to ambient light at temperatures ranging from 5 °C to 30 °C for 2 hours after being stored in vials for 0, 4 or 8 hours. Samples were tested for general appearance, pH, protein concentration, SEC, CGE, IL-5 binding, cIEF, particulate matter, and peptide mapping. Tables 3 and 4 (not copied in review) provide the results for syringes exposed to and protected from light, respectively. All results for both conditions at all temperatures met

the acceptance criteria, therefore DP is stable in the syringe for up to (b) (4)  
(b) (4)

**Reviewer comment (MAS):** The results demonstrate compatibility of DP in syringes during the course of normal administration. There was a minor increase in (b) (4) in samples exposed to light at 4 and 8 hours ( (b) (4) %) at the elevated temperature of 30°C. (b) (4)  
. This did not occur in syringes protected from light.

**6.5 Injectability with Different Needles:** This study examined the maximum force required to expel 1 mL of reconstituted DP to demonstrate the compatibility of the force to inject with the administered dose. Reconstituted DP was drawn up into 1 mL PP syringes with the following regular beveled needles: 21G 1 inch; 23 G 1 inch or 27 G ½ inch. The force to inject was measured with an Instron 3342 tensile tester using a displacement rate of 4 mm per second to mimic the speed of the plunger rod during manual injection.

Figure 1 (not copied in review), shows a typical injectability force profile using the Instron instrument and Table 5 (not copied in review) shows the results from the three different needed. The maximum force to expel the 1 mL reconstituted solution was 3.5 Newtons with the 27 G needle; lower than 30 N, which is considered to be the maximum limit for manual injection. (See Burckbuchler et al Eur J Pharm and Biopharm. 2010. In this paper high concentration polyclonal IgG was studied.) The maximum force for the 21 and 23 G needles was 2.2 and 1.9 N, respectively.

**Reviewer comment (MAS):** Overall, DP is compatible with the container closure and delivery devices under normal administration procedures.

### **3.2.P.3 Manufacture (MAS)**

#### **3.2.P.3.1 Manufacturer(s) (MAS)**

GlaxoSmithKline Manufacturing S.p.A., Parma, Italy: DP manufacture, primary and secondary packaging, DP release testing, batch release and stability testing.

Biopharmaceutical Central Testing Laboratories GlaxoSmithKline Medicines Research Centre Stevenage, UK DP release and stability testing.

#### **3.2.P.3.2 Batch Formula (MAS)**

A batch size ranges from (b) (4), resulting in (b) (4) vials. There are no overages.

**Table 2 Composition of Mepolizumab BDS**

Ingredient	Quantity <sup>1</sup>	Function
Mepolizumab (mg/mL)	(b) (4)	Drug Substance
Sucrose (b) (4)		(b) (4)
Sodium phosphate dibasic, heptahydrate (b) (4)		
Polysorbate 80 (b) (4)		
Water for Injection		

**3.2.P.3.3 Description of Manufacturing Process and Process Controls (MAS)**

(b) (4)

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**3.2.P.5 Control of Drug Product (MAS and JFS)****3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) (MAS)****Table 1 Specification for Mepolizumab for Injection, 100 mg/vial**

<b>Test</b>	<b>Method</b>	<b>Acceptance Criteria</b> For Release and Shelf Life Unless Noted as Different
<b>Appearance</b>		
Appearance <sup>1</sup>	Visual Observation Ph.Eur. 2.2.1, 2.2.2	White, uniform lyophilized cake.  Clear to opalescent, colorless to pale yellow or pale brown solution.  (b) (4)
Visible Particles <sup>1</sup>	Visual Observation Ph.Eur. 2.9.20	Essentially particle free solution after reconstitution
<b>General Tests</b>		
pH	USP <791> Ph.Eur. 2.2.3	(b) (4)
Particulate Matter	USP <788> Ph.Eur. 2.9.19	Particles $\geq$ (b) (4) $\mu\text{m}$ : $\leq$ (b) (4) particles/vial Particles $\geq$ (b) (4) $\mu\text{m}$ : $\leq$ (b) (4) particles/vial
Particulate Matter	Light Obscuration Particle Count Test	Particles $\geq$ (b) (4) $\mu\text{m}$ : Report results particles/vial
Residual Moisture	Karl Fischer Titration Ph.Eur. 2.5.32	Release $\leq$ (b) (4) Shelf-Life: (b) (4) %
Reconstitution Time <sup>1</sup>	Timed Examination	$\leq$ (b) (4) minutes
Weight Variation	USP <905> Ph.Eur 2.9.40	Release: Complies with USP and Ph.Eur
Osmolality	USP<785> JP 2.47	Release: (b) (4) mOsm/kg
<b>Quantity</b>		
Protein Concentration	Variable Pathlength UV/VIS	(b) (4) mg/mL
<b>Identity</b>		
Surface Plasmon Resonance (SPR)	IL5 Binding Assay	Identity confirmed
Capillary Isoelectric Focusing (cIEF)	Capillary Electrophoresis	Comparable to reference standard

Test	Method	Acceptance Criteria For Release and Shelf Life Unless Noted as Different
<b>Purity</b>		
Size Exclusion Chromatography (SEC)	Size Exclusion Chromatography	Release (b) (4)
		Shelf-Life (b) (4)
Reduced Capillary Gel Electrophoresis (CGE)	Capillary Gel Electrophoresis	% Purity $\geq$ (b) (4)%
Capillary Isoelectric Focusing (cIEF)	Capillary Electrophoresis	Comparable to Reference Standard % Main Peak $\geq$ (b) (4)% % Total Acidic $\leq$ (b) (4)%
<b>Potency</b>		
IL-5 Neutralization	Bioassay	ED50 Ratio (Standard/Sample) $\geq$ (b) (4)
Surface Plasmon Resonance (SPR)	IL-5 Binding Assay	Specific Binding Activity (b) (4)
<b>Safety</b>		
Endotoxin	USP <85> Ph.Eur 2.6.14 FDA LAL Guideline <sup>2</sup>	Release: $\leq$ (b) (4) EU/mg
Sterility	USP <71> Ph.Eur 2.6.1 21 CFR 610.12	Release: Passes test End of Shelf Life: Passes test
Container Closure Integrity <sup>3</sup>	Dye Immersion Test	Shelf-Life: Passes test

1. The product is reconstituted with 1.2 mL of water for injection (WFI).
2. Guideline on Validation of the Limulus Amebocyte Lysate Test as an End Product Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices” [FDA, December 1987].
3. Container Closure Integrity test not performed at release.

The proposed commercial specifications took into account the release and stability data from (b) (4) MDP1 and (b) (4) MDP2 lots and clinical experience. The 4-step statistical approach was described in S.4.3. As for DS, only (b) (4) by SEC showed a significant change over 60 months. Therefore the DP release criteria were calculated using the EOSL acceptance criteria plus total degradation during the DP Shelf Life. For monomer this would be DP EOSL Spec – (b) (4)

**Reviewer comment (MAS):** I asked Dr. Swisher to analyze the release and stability data for the (b) (4) and MDP1/2 lots to determine if we can agree with GSK's justification of the specifications for each method. She focused on the DP stability data for samples stored at 5°C for pH, SEC (b) (4) R-CGE, and the IL5 neutralizing assay and ran the analysis using GraphPad Prism. Using this program she determined the (b) (4) SD vs. 95% confidence or prediction intervals ((b) (4) %), which were used by GSK. The linear regression analysis for these methods showed no significant slope and it was determined that the specifications are justified. Because the data for the (b) (4) lots are similar to those for the MDP1/2 lots, the DS data were not analyzed by GraphPad Prism.

As noted below, the read out for the IL5 neutralization assay has shifted upwards since it was transferred to BioCTL and there appears to be greater variability at this site as well. The MDP1 and pilot lot data were graphed separately from the MDP2 lots because of this. The MDP1/pilot lot data had no significant downward trend over 60 months. The MDP2 data only go out to 18 months at this time and because of the variability, it is difficult to discern a trend.

Table 1, not copied in review, provides the approach use to establish the acceptance criteria for each method (based on compendial requirements, results from clinical batches, target  $\pm$  range, process and safety considerations, statistical analysis), the lots included in the analysis and the rationale for the lots included. Table 2 (not copied in review), shows that data from 8 pilot lots, 13 MDP lots and 9 MDP2 lots were used to establish the acceptance criteria.

**Appearance:** Proposed Commercial Acceptance Criteria: White, uniform lyophilized cake. Clear to opalescent, colorless to pale yellow or pale brown solution. (b) (4)

**Visible Particles:** Essentially particle free solution after reconstitution. Acceptance criteria are based on results from 1 MDP1 and 10 MDP2 lots.

**pH:** Proposed Commercial Acceptance Criteria: (b) (4) Acceptance criteria are based on results from all the lots listed in Table 2 and are presented in Figure 2, not copied in review.

**Reviewer comment (MAS):** The upper limit of pH (b) (4) is reasonable given the data in Figure 2 shows one lot with a result between (b) (4). The lower limit of pH (b) (4) seems generous given that no lot had a pH lower than (b) (4). However, the range in general is acceptable.

**Particulate Matter:** Proposed Commercial Acceptance Criteria: Particles (b) (4) particles/vial; Particles  $\geq$  (b) (4) particles/vial; Particles  $\geq$  (b) (4)  $\mu\text{m}$  : Report results particles/vial.

**Reviewer comment (MAS):** This is a compendial standard for (b) (4). There are no established criteria for the smaller particles, but sponsors are asked to assess them and report the results. GSK is doing this.

**Residual moisture:** Proposed Commercial Acceptance Criteria: Release:  $\leq$  (b) (4) %; Shelf-Life:  $\leq$  (b) (4) %. Acceptance criteria are based on results from all the lots listed in Table 2 and are presented in Figure 3, not copied in review.



**Reviewer comment (MAS):** *No specific data from any lots are mentioned. However, this is okay – the data confirming identity are provided with the batch release data and the method validation is acceptable.*

(b) (4)



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**Endotoxin:** Proposed Commercial Acceptance Criteria:  $\leq$  (b) (4) EU/mg.

Throughout development, endotoxin levels have consistently been below  $\leq$  (b) (4) EU/mg. Using the USP <85> and Ph.Eur.2.6.14 compendial maximum allowed endotoxin limit calculations for a 70 kg person or an adolescent weighing ~ 40 kg, the endotoxin limits are (b) (4) EU/mg and (b) (4) EU/mg, respectively. The proposed criterion is well below both limits, and is consistent with the clinical specification and manufacturing history.

**Sterility:** Proposed Commercial Acceptance Criteria: Passes test – confirmed sterile according to 21CFR610.12, USP <71> and EP 2.6.1. This is performed at release and EOSL.

### 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (JFS)

**Reviewer comment (MAS):** *The endotoxin, sterility and CCI methods and method verifications are deferred to DMA/OPF. JFS reviewed all other methods and their verification or validation. Note that IR #2 questions 8 b and 8c dated 3/4/15, requested descriptions of the compendial methods and the verification of the methods, questions 8d and 8f requested additional information regarding the IL5 neutralization assay and question 8e asked for clarification of the methods performed at BioCTL versus Parma. Regarding question 8e, GSK clarified in their response to IR#2 dated 4/1/15, that Weight Variation, Osmolality, and Container Closure Integrity were performed at the Parma site. Methods that are used for both DS and DP are described in S.4. The non-compendial methods for DP are reconstitution time, IL5 neutralization bioassay, and container closure integrity testing. Descriptions of the compendial methods and the verification were also provided.*

**Reconstitution Time:** The method to determine reconstitution time was validated at

- (b) (4)
- 
- 

Co-validation transfer of this method was conducted according to protocols INS\_199632 and INS\_181273 to the BioCTL and Parma labs. Mepolizumab DP lots ENG-2001 and ENG-2002 (Parma) and EE603641 (BioCTL) were used.

DP samples are removed from 2-8° C storage, allowed to reach room temperature ( $\geq$  30 minutes) and reconstituted with 1.2 mL of WFI or water equivalently purified. After water is added, the vial is swirled for 10 seconds with circular motion at 15-second intervals until all visible pieces are dissolved, checking every 15 seconds. Results are converted to minutes.

The assay was performed by two analysts from Parma, one from BioCTL, and one from (b) (4) on two occasions each. On each occasion, three DP vials were reconstituted per lot for each of two DP lots (six vials total) to generate two reportable results, each the mean result of triplicate reconstitutions.

The method was validated for repeatability (intra-assay), intermediate precision (intra-laboratory), reproducibility (inter-laboratory), laboratory equivalence (mean absolute difference between labs must be  $\leq$  (b) (4) minutes) and robustness.

**Reviewer comment (JFS):** The %RSD for intra-assay, intra-lab, and inter-lab comparisons all easily met the acceptance criteria. The mean absolute difference between labs also met the acceptance criterion of  $\leq$  (b) (4) minutes; reconstitution took longer at BioCTL and Parma than at (b) (4) by (b) (4) minutes on average, respectively.

Robustness of the assay was studied to understand the effect of temperature on reconstitution time, as DP is to be taken from 2-8° C storage and allowed to equilibrate for 30 minutes at room temperature prior to addition of WFI. The mean absolute difference between reconstitution time at 2-8° C and room temperature was (b) (4) minutes, demonstrating that the assay is robust with regard to temperature. This method was validated successfully for its intended use.

**Visible Particulates and Particulate Matter:** Visible particle testing complies with EP 2.9.19 and particulate matter testing complies with USP<788> and EP 2.9.19. Samples are reconstituted and visibly examined while gently swirling in front of black and white background for five seconds each. Using the light obscuration method for particles  $\geq 10 \mu\text{m}$ ,  $\geq 25 \mu\text{m}$ , or 2-10  $\mu\text{m}$ , environmental testing of water and glassware are first conducted. Then, reconstituted samples are combined to a volume of not less than 25 mL DP. Sample is degassed and then measured for each particle size.

**Reviewer comment (JFS):** The methods were verified successfully and are suitable for their intended use.

**Residual Moisture:** The residual moisture method complies with compendial method EP 2.5.32 and involves the release of moisture through heating and a Karl Fischer (KF) colorimetric titration. The results ranged from (b) (4) % moisture w/w, which met the acceptance criterion of  $\leq$  (b) (4) % w/w.

**Reviewer comment (JFS):** The verification of this compendial method was performed at GSK GMS BioCTL using one DP batch assayed by two analysts during two occasions each, making three determinations on each occasion. This assay has been verified and is suitable for its intended purpose.

**Weight Variation:** This method to determine the uniformity of dosage units complies with USP<905> and EP 2.9.40. The test is performed using ten drug product vials; each vial is weighed, then reconstituted, then all reconstituted product is removed for drying of the stopper and vial. The weight of the lyophilized cake is the difference between the vial with the lyophilized cake and the empty, dried vial.

The average % Label Claim and standard deviation(s) for the 10 vials are calculated and acceptance value is determined. The batch passes if the acceptance criteria of  $AV \leq$  (b) (4) are met. If the AV is (b) (4) or greater, an additional 20 vials are tested. If the  $AV \leq$  (b) (4) and no single vial is greater than (b) (4) or less than (b) (4) of the reference value, then the batch passes.

This method was tested at GSK Parma using DP and passed the compendial acceptance criteria.

**Reviewer comment (JFS):** The verification of this compendial method was reasonable and all parameters passed. This assay is suitable for its intended purpose.

**Osmolality:** This method complies with USP <785>. Freezing point depression is used to assess osmotic strength and instrument calibration is verified daily using at least one standard. Sample measurement must generate a %RSD  $\leq$  (b) (4)%, and calibration following sample reading must be performed with a sample within (b) (4) mOsm/kg of the expected sample value and measurements must be within (b) (4) mOsm/kg of the standard and %RSD  $\leq$  (b) (4)%.

**Reviewer comment (JFS):** *This test was verified at GSK Parma using two DP batches assayed by two analysts on one occasion each with three determinations of osmolality on each occasion per batch. The verification of this compendial method was reasonable and all parameters passed. This assay is suitable for its intended purpose.*

(b) (4)

**Reviewer comment (JFS):** This assay could possibly be stability-indicating, although DP stability studies do not support this. In addition, increased assay variability at BioCTL makes it even less likely that this assay would be useful as a stability-indicating method.

Although the acceptance criterion of  $R^2 \geq$  (b) (4) is relatively broad, the actual linearity of this assay is reasonable for a bioassay and is acceptable.

(b) (4). Therefore, the validation of the IL5 neutralization bioassay at BioCTL appears acceptable.

**Reviewer comment (MAS):** None of the lots used to validate the method were MDP2 lots. There is a shift in the results for MDP2 lots seen at BioCTL. However, this appears to be due to (b) (4) rather than the method itself. See reviewer comments under Justification of Specification.

#### 3.2.P.5.4 Batch Analyses (MAS)

Data are provided for 9 MDP2 batches, including the 3 PPQ batches, manufactured by the commercial process. All were released using the current and updated methods on the proposed commercial specification. In addition, MDP2 batch 3501 was also tested with the legacy methods to provide an analytical bridge to protein concentration by fixed pathlength UV/VIS, SDS-PAGE, IEF, and IL5 binding ELISA.

Batch analysis results also include NR-CGE and percent basic peaks by cIEF, which are not included in the proposed commercial specifications. However, these were in place for release of clinical lots and at the time these lots were released. They are also part of the ongoing registration stability studies.

Besides the 9 MDP2 batches, data are provided for 13 MDP1 batches and 14 pilot scale batches (three from (b) (4), five from (b) (4) and six from (b) (4) batches). Table 1 (not copied in review) provides a summary of the DP batches, the date and site of manufacture, DS genealogy and DP batch uses (stability, pre-clinical, clinical, PPQ). Batch analysis tables 2-9 (not copied in

review provide data for MDP2 lots (Tables 2 and 3), MDP1 (Tables 4-6) and pilot lots (Table 7-9).

**Reviewer comment (MAS):** All batches met release criteria in place at the time of release using methods in place at time of release. The criteria for reconstitution time increased over the course of development from (b) (4) minutes to the current (b) (4) minutes. This probably reflects the (b) (4) Other than that change, other attributes such as % (b) (4) have been remarkably consistent across all manufacturing processes.

**3.2.P.5.5 Characterization of Impurities (MAS)**

There are no new impurities in DP. See S.3.2.

**3.2.P.6 Reference Standards or Materials (MAS)**

See S.5

**3.2.P.7 Container Closure System (MAS)**

Table 1 provides details of the container closure components. Letters for Authorization for each DMF are provided.

**Table 1 Description of Packaging Components and Respective Manufacturers**

Component	Description	Manufacturer	DMF Number
Vial	10-mL, Type 1 glass vial	(b) (4)	(b) (4)
Rubber stopper	(b) (4) gray, (b) (4) rubber, (b) (4) stopper		
Overseal	(b) (4) overseal with a matte red plastic flip-off cap		

Representative drawings and information on the dimension for each component are provided in Figures 1-3 and Tables 2-4 (not copied in review).

The glass vials and rubber stoppers meet pharmacopeial requirements.

The container closure components are provided by qualified suppliers who are audited prior to the initial purchase. Supplier qualification is a continuous process that is monitored through quality performance and periodic audits. Components are tested upon receipt until supplier reliability is established, after which a reduced testing program may be implemented with acceptance of the supplier’s CoA. Changes to the components by the supplier are subject to a change control system agreed upon by GSK and the supplier.

Upon receipt at GSK, materials are sampled according to an approved sampling plan. Table 5 (not copied in review), provides methods for testing each component and the specification for each method. These include compendial requirements, visual inspection, defects and dimensional control. Figures 4 and 5 (not copied in review) show IR spectra of the internal and surface material of the rubber stoppers.

### **3.2.P.8 Stability (MAS)**

#### **3.2.P.8.1 Stability Summary and Conclusion (MAS)**

**Reviewer comment (MAS):** GSK initially requested an expiration date of (b) (4) months for mepolizumab DP based on real time MDP1 stability data. They provided a statistical comparison of the MDP1 and MDP2 data to support this. (b) (4)

(b) (4) the lyophilization cycle has been optimized for the MDP2 process. A consult request was submitted to the Office of Biostatistics on January 16, 2015 to review the statistical analysis of the forced degradation comparability study, with a requested completion date of April 3, 2015. Dr. Dong, who reviewed the statistical analysis, did not find the analysis to be adequate, in part because there were only 12 months of real time MDP2 data compared with 60 months of data for MDP1 lots. IR#3, sent on 4/9/15, requested a justification for the MDP1 container closure to be considered representative of the MDP2 container closure. In their response to the IR, dated 5/14/15, GSK provided updated MDP2 stability out to 18 months and requested an expiration dating period of 24 months. The statistical analysis has been removed from the BLA, since GSK agreed it is of limited value.

Overall, I agree that the data support an expiration dating period of 24 months when stored at (b) (4) (b) (4) 25°C ± 2°C/60%±5% RH (≤25°C) protected from light. (b) (4)

(b) (4)

(b) (4)

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the need of bioburden sampling; however, (b) (4)

he bioburden sampling may be adequate.

10

(b) (4)

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

**IR #4 (RCC, status update to IR#1 7c and 7d, 1-2; MAS 3) sent April 9, 2014, responses received June 10, 2015:**

#### **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:

1. Submit endotoxin limits for the (b) (4).
2. Include bioburden and endotoxin as part of the (b) (4)

#### **Product Quality – Drug Product**

3. Submit the IL5 neutralization transfer summary and provide an update into the investigation regarding the shift in assay performance upon transfer of the method to BioCTL. Finally, indicate the lots in Figure 15 (Section 3.2.P.5.6 Justification of Specifications) that were tested at BioCTL or at the GMS Analytical Testing Laboratory in Parma.

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

**Application #: 125526**      **Submission Type: BLA**      **Established/Proper Name: mepolizumab**  
**Applicant: GlaxoSmith Kline LLC**      **Letter Date: November 5, 2014**      **Dosage Form: lyophilized powder for reconstitution**  
**Chemical Type: Monoclonal Antibody**      **Stamp Date: November 4, 2014**      **Strength: 100 mg/vial**

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>			
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	Yes		Fileable
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?	Yes		Need details of compendial methods used for drug substance and drug product and drug product microbial controls

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity <sup>1</sup>	X	<input type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	X	
3.	Naturally-derived Product	<input type="checkbox"/>	X	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	X	
5.	PET Drug	<input type="checkbox"/>	X	
6.	PEPFAR Drug	<input type="checkbox"/>	X	
7.	Sterile Drug Product	X	<input type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	X	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	X	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	X	
11.	Lyophilized product <sup>1</sup>	X	<input type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	X	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	X	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	X	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	X	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	X	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	X	
18.	Combination Product	<input type="checkbox"/>	X	
19.	Other _____	X	<input type="checkbox"/>	Humanized Monoclonal Antibody

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
<b>Regulatory Considerations</b>				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Quality Considerations</b>				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

<b>C. FILING CONSIDERATIONS</b>					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

<b>C. FILING CONSIDERATIONS</b>					
	<input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>				
<b>FACILITY INFORMATION</b>					
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: <ul style="list-style-type: none"> <li><input type="checkbox"/> Name of facility,</li> <li><input type="checkbox"/> Full address of facility including street, city, state, country</li> <li><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</li> <li><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</li> <li><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</li> <li><input type="checkbox"/> DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <li><input type="checkbox"/> Is a manufacturing schedule provided?</li> <li><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>DRUG SUBSTANCE INFORMATION</b>					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input type="checkbox"/>	<input type="checkbox"/>	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? <ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

<b>C. FILING CONSIDERATIONS</b>				
	<ul style="list-style-type: none"> <li>○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li>○ Includes complete description of product lots and their uses during development – BLA only</li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance                             <ul style="list-style-type: none"> <li>○ 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)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> </li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability                             <ul style="list-style-type: none"> <li>○ 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</li> </ul> </li> </ul>			<p>Descriptions of compendial methods are not provided. This information will be requested.</p>
<b>DRUG PRODUCT INFORMATION</b>				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots</li> <li>○ Includes complete description of product lots and their uses during development</li> </ul> </li> <li><input type="checkbox"/> Manufacture                             <ul style="list-style-type: none"> <li>○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> </li> <li><input type="checkbox"/> Control of Excipients</li> <li><input type="checkbox"/> Control of Drug Product                             <ul style="list-style-type: none"> <li>○ Includes production data on drug product</li> </ul> </li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>
				<p>In controls of critical steps and intermediates (P3.4), microbial controls</p>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	<p>manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</p> <ul style="list-style-type: none"> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>○ 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)</li> <li>○ Analytical validation package for release test procedures, including dissolution</li> </ul> <p><input type="checkbox"/> Reference Standards or Materials</p> <p><input type="checkbox"/> Container Closure System</p> <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> <p><input type="checkbox"/> Stability</p> <ul style="list-style-type: none"> <li>○ 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</li> </ul> <p><input type="checkbox"/> APPENDICES</p> <p><input type="checkbox"/> REGIONAL INFORMATION</p>				<p>were not included. This information will be requested.</p>
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> <li>• Does the application contain the complete BA/BE data?</li> <li>• Are the PK files in the correct format?</li> <li>• Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	X	
9.	<p>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? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	Comparability has been demonstrated throughout development
10.	<p>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.</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
11.	<p>For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
12.	<p>For an extended release dosage form, is there enough information to assess the extended release</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	designation claim as per the CFR?				
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <li><input type="checkbox"/> facilities and equipment                             <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing flow; adjacent areas</li> <li><input type="checkbox"/> other products in facility</li> <li><input type="checkbox"/> equipment dedication, preparation, sterilization and storage</li> <li><input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination</li> </ul> </li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:                             <ul style="list-style-type: none"> <li><input type="checkbox"/> avoidance and control procedures</li> <li><input type="checkbox"/> cell line qualification</li> <li><input type="checkbox"/> other materials of biological origin</li> <li><input type="checkbox"/> viral testing of unprocessed bulk</li> <li><input type="checkbox"/> viral clearance studies</li> <li><input type="checkbox"/> testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <li><input type="checkbox"/> 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:                             <ul style="list-style-type: none"> <li><input type="checkbox"/> LAL instead of rabbit pyrogen</li> <li><input type="checkbox"/> Mycoplasma</li> </ul> </li> <li>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</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**OFFICE OF PHARMACEUTICAL QUALITY**  
**FILING REVIEW**

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Jennifer Swisher, Ph.D., Division of Monoclonal Antibodies, Office of Biotechnology Products

**Jennifer F. Swisher**  
**-S**

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ou=People, 0.9.2342.19200300.100.1.1=1300387073,  
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Maria Candau-Chacon, Ph.D., Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality

**Maria D.**  
**Candauchacon -S**

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cn=Maria D. Candauchacon -S  
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Candace Gomez-Broughton, Ph.D., Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality

**Candace Y. Gomez-**  
**broughton -S**

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cn=Candace Y. Gomez-broughton -S  
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Patricia Hughes, Ph.D., Team Leader, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality

**Patricia F.**  
**Hughestroost -S**

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cn=Patricia F. Hughestroost -S  
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Marjorie Shapiro, Ph.D., ATL, Division of Monoclonal Antibodies, Office of Biotechnology Products

**Marjorie A.**  
**Shapiro -S**

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ou=FDA, ou=People,  
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cn=Marjorie A. Shapiro -S  
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