CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761070Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA/BLA 070

BLA-761070-ORIG-1

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Project Owner
Kelly Ballard
REGULATORY HEALTH PROJECT M

Nov 15, 2017 | Current | At Risk | 64.33%

Project Summary | Executive View | Application Life Cycle | Consults | Documents (24) | Archive | **Inspection View**

Inspection View (New Drugs)

As of Nov 9, 2017 2:23 pm Eastern Standard Time

Inspection View (New Drugs)

Task Numbe ↑	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)								
7	Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.	Kelly Ballard IM - Filing PM/Coordinator	11/20/16	11/21/16	Complete	Go to Form	
43	Overall Manufacturing Inspection Recommendation			11/15/17	9/19/17	Complete	Go to Form	Recommendation: Approve
Parent: Facility: (b) (4) **FACILITY STATUS: PENDING (1)**								
10	Enter Profile Codes		Zhong Li IM - Facility Profile Reviewer Facility Profile Reviewer	11/25/16	11/28/16	Complete	Go to Form Go to Program	
Parent: Profile Evaluation for (b) (4) **FACILITY STATUS: PENDING (5)**								

Showing

Wally Bepler

10/18/17 Report

BLA-761070-ORIG-1 : Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

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/s/

ASHLEY N WALLACE
11/17/2017

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: Medimmune, LLC
City, State: Gaithersburg, MD
EI Dates: September 18-20, 2017
FDA Participants: John Dan, Investigator, ORA-OBIMO-DBIMO 1
Charles R. Bonapace, Pharm.D., Pharmacologist, CDER-OSIS

Inspection Summary

This FY2017 inspection was the first FDA GLP inspection of Medimmune, LLC. Two GLP studies were audited during the inspection. At the close-out meeting, no Form FDA 483 was issued; however, two items were discussed with the management. The first discussion item pertained to the possibility of employees using SOPs without adequate training because there were gaps between the approval and effective dates of SOPs. The second item pertained to inadequate documentation of method validation studies with large molecules, where the run acceptance criteria was (b) (4) % of the accuracy and precision instead of the usual (b) (4) %. The final classification of the inspection is No Action Indicated (NAI). I recommend that the data from the audited studies and other studies of similar design conducted at Medimmune, LLC be accepted for Agency review by the pertinent review divisions.

Studies Audited during this Inspection

(b) (4) Study No.: AAO00095
Study Title: A 9-Month Intravenous and Subcutaneous Dose Toxicity, Toxicokinetics, and Immunogenicity Study of MEDI-563 in Cynomolgus Monkeys with a 12-Week Recovery Period
Study Initiation Date: February 6, 2009
Final Report Date: February 3, 2011

(b) (4) Study No.: AAO00036
Study Title: Maternal, Embryo-Fetal and Neonatal Toxicity Study of MEDI-563 Administered Bi-Weekly by Intravenous Injection to Pregnant Cynomolgus Monkeys, Including a 6.5 Month Postnatal Evaluation
Study Initiation Date: November 11, 2008
Final Report Date: April 19, 2011

Test Article: MEDI-563, Benralizumab
Testing Facility: (b) (4)
Sponsor: AstraZeneca Pharmaceuticals, LP (Gaithersburg, MD)

Relevant FDA Applications: BLA-761070
IND 100237 (Submitter in DARRTS: Medimmune, LLC)
Review Divisions: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) (BLA-761070 and IND 100237)

Background: Medimmune, LLC is a research, bioanalytical and histopathology laboratory. Histopathology peer review is also conducted at this facility. However, there are no animals housed at the facility and no clinical pathology work is conducted. (b) (4)

Prior Inspection: There are no prior GLP inspections conducted by FDA of this firm.

Current Inspection: This initial inspection conducted by FDA was a FY2017 GLP Directed Inspection performed at the request of the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory counterpart of the FDA. The PMDA requested two GLP studies be audited to ensure they were conducted in accordance with 21 CFR part 58 Good Laboratory Practice (GLP) regulations and to determine the quality and integrity of data generated for the portions of the two audited studies conducted by Medimmune, LLC.

The current inspection included a tour of the bioanalytical laboratory facilities and facility operations, standard operating procedures (SOPs), equipment, employee qualifications and training, Quality Assurance Unit (QAU) operations, management responsibilities and recordkeeping systems, archiving operations, training records for relevant staff, and correspondence between the sponsor and testing facility. In addition, the method validation and sample analysis from the toxicokinetic (TK) portion of both studies were audited during the inspection.

Although Form FDA 483 was not issued at the inspection closeout meeting, two items were discussed with the firm's management. The discussion items and my evaluation follow.

1) Training for laboratory SOPs is not always provided to relevant staff before the effective date. The gap between an SOP's finalization date and its effective date has the potential to allow employees to begin using the current version of an SOP without receiving adequate training.

During the inspection, the firm stated that, beginning in Fall 2017, SOP training will be provided to relevant staff when an SOP is finalized and before its effective date to eliminate the possibility that an employee is inadequately trained when an SOP becomes effective.

OSIS Evaluation: The firm promised to provide training on all SOPs prior to the effective date beginning in Fall 2017. Thus, the corrective action should prevent this finding from recurring in future studies under similar circumstances. Because no instances of inadequate training on SOPs were observed during the inspection, this discussion item does not impact the quality and integrity of studies conducted by Medimmune, LLC.

2) During the method validation of the ELISA assay for quantification of MEDI-563 in cynomolgus monkey serum, documentation of changes to the run acceptance criteria from within (b) (4) % to within (b) (4) % was not fully transparent.

During the inspection, the firm stated that the acceptance limits were widened from within (b) (4)% to within (b) (4)% because the ELISA analytical method had a limited optical density span, which limits the method's ability to consistently perform within (b) (4)% accuracy and precision.

OSIS Evaluation: Although widening acceptance limits to within (b) (4)% from the accepted within (b) (4)% could impact the quality and integrity of data generated with this bioanalytical method, the conduct and results of the method validation were accurately reported in the method validation report and the impact of widening the acceptance criteria are not significant enough to alter the study outcome.

Recommendations:

- After evaluating the inspectional findings, the data from the two audited studies were found to be reliable. Thus, I recommend that studies AAO00036 and AAO00095 be accepted for Agency review.
- The data from studies with similar design conducted before the end of the surveillance interval should be accepted for Agency review without an inspection.
- The next inspection should be scheduled in three years.
- Final classification: No Action Indicated (NAI).

Abhijit Raha, Ph.D.
Pharmacologist

Charles R. Bonapace, PharmD
Director, DNDBE

Date Assigned: 07/02/2017
EI Dates: 09/18/2017 through 09/20/2017
District Office: Baltimore (BIMO-East)
FDA Investigators: John Dan, ORA-OBIMO-DBIMO 1
Charles R. Bonapace, Pharm.D., CDER-OSIS

Inspection Type: _____Routine Surveillance __X__Directed (For Cause)
FDA-483 Issued: __X__No _____Yes
Letter Issued: __X__None _____Inspection Close-Out Letter

Date EIR Assigned to Reviewer: 10/23/2017 (retrieved from OSAR database)
1st Draft Review Completed: 10/26/2017

Inspection Conclusion: NAI
District Decision: NAI
Final HQ Classification: NAI

cc: via DARRTS

OSIS/Kassim/Nkah/Fenty-Stewart/Miller/Johnson
OSIS/DNDBE/Bonapace/ChenZ/Raha
DPARP/Timothy W. Robison/Pharmacologist (BLA-761070 and IND 100237)
DPARP/Colette C. Jackson/Regulatory Project Manager (BLA-761070 and IND 100237)
HFR-CE100/Anne E. Fenton-Johnson/Head, Division of BIMO Operations I (BIMO East, PHI-DO)
HFR-CE150/John Dan (ORA Investigator) (Division of BIMO Operations I, OBIMO, BLT-DO)
Draft: AR 10/26/2017, 10/29/2017, 11/01/2017
Edits: ZC 10/27/2017; SYK 10/27/2017; CB 10/31/2017
OSIS File: GLP0976
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/GLP Program/Medimmune, LLC, Gaithersburg, MD/ FY2017/ REVIEW (EIR COVER)

APPEARS THIS WAY ON ORIGINAL

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/s/

ABHIJIT RAHA
11/01/2017

ZHOU CHEN
11/01/2017

CHARLES R BONAPACE
11/01/2017

SEAN Y KASSIM
11/01/2017

First Approval for Indication

Recommendation: Approval

BLA 761070
Review

Date: September 29, 2017

From: Jennifer Swisher, Ph.D.
Team Leader, DBRR I/OBP/OPQ

Sarah Kennett, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Through: Kathleen Clouse, Ph.D.
Director, DBRR I/OBP/OPQ

Drug Name/Dosage Form	**Fasenra (benralizumab)/injection**
Strength/Potency	**30 mg/1.0 mL prefilled syringe**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype**
Applicant/Sponsor	**AstraZeneca AB**
US agent, if applicable	**AstraZeneca Pharmaceuticals LP**

Product Overview

Benralizumab is a humanized afucosylated IgG1κ monoclonal antibody produced in CHO cells. Benralizumab targets the α chain of the IL-5 receptor (IL-5Rα) and when bound to IL-5Rα on eosinophils (or other IL-5Rα positive cells), 1) blocks the binding of IL-5 to the IL-5 receptor and downstream signaling and 2) activates ADCC, leading to a reduction in eosinophil levels. Benralizumab drug product is supplied at 30 mg/1.0 mL as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in pre-filled syringes (PFS). Benralizumab is proposed as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jennifer Swisher	DBRR I/OBP/OPQ
Drug Product	Jennifer Swisher	DBRR I/OBP/OPQ
Immunogenicity	Jennifer Swisher	DBRR I/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Zhong Li	DIA/OPF/OPQ
Microbiology (DS)	Maria Jose Lopez-Barragan	DMA/OPF/OPQ
Microbiology (DP)	Candace Gomez-Broughton	DMA/OPF/OPQ
Business Process Manager	Kelly Ballard	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Sarah Kennett	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Kathleen Clouse	DBRR I/OBP/OPQ
Microbiology Team Lead	Maria Reyes Candau-Chacon Dupeh Palmer	DMA/OPF/OPQ DMA/OPF/OPQ
Facilities Team Lead	Zhihao Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Colette Jackson	DPARP/ODEII/OND
Cross-disciplinary Team Lead	Lydia Gilbert McClain	DPARP/ODEII/OND
Medical Officer	Sofia Chaudhry	DPARP/ODEII/OND
Pharm/Tox	Timothy Robison	DPARP/ODEII/OND
Clinical Pharmacology	Sury Sista	DPARP/ODEII/OND
Stats	Yu Wang	DBII/OB/OTS

a. Names
   i. Proprietary Name: Fasenra
   ii. Trade Name: Fasenra
   iii. Non-Proprietary/USAN: benralizumab
   iv. CAS name: 1044511-01-4
   v. INN Name: benralizumab
   vi. OBP systematic name: MAB HUMANIZED (IGG1) ANTI Q01344 (IL5RA_HUMAN) [MEDI563]

b. Pharmacologic category: Interleukin-5 receptor alpha-directed cytolytic monoclonal antibody

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Branch Chief	Patricia Hughes	See Panorama
Facilities Branch Chief	Peter Qiu	See Panorama
Team Lead OBP/DBRRI	Jennifer Swisher	See Panorama
Director OBP/DBRRI	Kathleen Clouse	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761070/0000	11/16/2016	OBP, DMA, DIA
761070/0011	4/4/2017	OBP, DMA, DIA
761070/0016	5/25/2017	OBP
761070/0019	6/30/2017	OBP
761070/0020	7/10/2017	OBP, DMA
761070/0024	8/11/17	OBP
761070/0028	9/1/17	OBP
761070/0030	9/25/17	OBP

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]
(b) (4)				1	Adequate
				1	Adequate
				3	N/A
				3	N/A
				3	N/A

[1] Action codes for DMF Table: 1 – DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

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

C. Other Documents: None

3. CONSULTS: CDRH re syringe system

Product Quality Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761070 for Fasenra (benralizumab) manufactured by AstraZeneca AB. The data submitted in this application are adequate to support the conclusion that the manufacture of benralizumab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Approval action letter language

- Manufacturing location:
  - Drug Substance – AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center, Frederick, MD
  - (b) (4)
  - Drug Product manufacturing, labeling, and packaging– (b) (4)
- Fill size and dosage form – 30 mg/mL, injection, single-dose prefilled syringe
- Dating period:
  - Drug Substance: (b) (4) months; (b) (4) °C
  - (b) (4)
  - Drug Product: 24 months; 2-8°C
  - Protocols for the extension of DS and DP expiry periods are approved
- Exempt from lot release
  - Yes. Exemption of specified products according to 601.2a

c. Benefit/Risk Considerations

Benralizumab is proposed as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. Two other antibody products, mepolizumab and reslizumab, have recently been approved for the same indication. While the specific mechanisms by which these antibodies function are not exactly the same, they target the same cell types and general signaling pathways (i.e., eosinophils that express and are impacted by IL-5 receptor). Benralizumab binds to the α subunit of human IL-5R and to FcγRIIIa and mediates ADCC activity. In addition, it blocks the binding of IL-5 to the receptor. IL-5R is expressed on eosinophils and basophils, and IL-5 is a hematopoietic cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils. Eosinophilic inflammation is common in asthma, and eosinophils and basophils are thought to play key roles in the pathogenesis and severity of asthma. Increased levels of eosinophils have been found in the airways of patients with chronic bronchial asthma. Administration of benralizumab, mepolizumab, or reslizumab leads to depletion of eosinophils, and the currently approved products provide clinical benefit.

The overall control strategy for benralizumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of Drug Substance (DS), (b) (4) and Drug Product (DP), and stability of these materials. The Office could not initially recommend approval of benralizumab due to the availability of other products for the proposed indication and a lack of support for DP (b) (4) and sterility assurance, as well as numerous additional issues with the DS, (b) (4) and DP control strategy that remained following numerous communications between the applicant and the Agency. Aspects of the control strategy for which there remained unresolved issues included batch release and stability specifications, expiry periods for the DS and DP, Reference Material (RM) qualification, Working Cell Bank (WCB) qualification and cell bank stability, DS manufacturing process parameters, (b) (4) protocols, and raw material controls. However, additional data and information have been submitted to the BLA to mitigate these issues, and the currently proposed manufacturing control strategy, in-process controls, process monitoring tests, release, and stability testing is sufficient to ensure process consistency and DS, (b) (4) and DP that have appropriate quality and are free of adventitious agents.

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

To perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance, (b) (4) and drug product.

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Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Drug Substance (DS), (b) (4) and Drug Product (DP) CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, deamidation, and fragmentation. Minimal change is expected during storage through expiry.	(b) (4)	No CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Safety/Immunogenicity and potentially PK	Manufacturing process and exposure to heat stress. Minimal change is expected during storage through expiry.		
Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat and potentially extreme light stress.		N/A

		A small increase in fragments is expected during (b) (4) DP storage.	(b) (4)	
Glycosylation (b) (4)	Efficacy (ADCC activity/FcγRIIIa binding)	(b) (4) No change is expected during storage.		(b) (4)
Glycosylation (b) (4)	PK	(b) (4) No change is expected during storage.		
Heavy chain (b) (4)	Efficacy(FcγRIIIa binding) and potentially PK (FcRn binding)	Manufacturing process and exposure to heat stress. Minimal change is expected during storage under recommended conditions.		It is not clear how (b) (4) occurs under some heat stress conditions; therefore, appropriate controls should be implemented.
Heavy Chain (b) (4)	PK (FcRn binding)	Manufacturing process and exposure to heat and light		Requires substantial

(b) (4)		stress. Minimal change is expected under recommended storage conditions.	(b) (4)	stress to generate a clinically meaningful impact.
Osmolality	Safety, Efficacy (b) (4)	Formulation		N/A
pH	Safety and Efficacy	Formulation		N/A
Protein Content	Efficacy	Manufacturing process		N/A
Polysorbate 20	Safety and efficacy (b) (4)	Formulation		N/A

B. Drug Substance [benralizumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (4)		N/A

			(b) (4)	
Residual (b) (4) (Process-related impurity)	Safety	(b) (4)		
Residual (b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during (b) (4)		N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during (b) (4)		N/A
Leachables (Process-related	Safety	Process-related impurities potentially from manufacture and		N/A

impurity)		the DS container closure system	(b) (4)	
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through raw materials and throughout the manufacturing process		N/A

a. Description

Benralizumab is a recombinant, humanized afucosylated IgG1κ monoclonal antibody and consists of two heavy chains that are each composed of 451 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 301 (Asn301). The molecular weight of deglycosylated benralizumab without C-terminal lysine is 144,801 Da.

The extinction coefficient was calculated and confirmed experimentally to be 1.43 $(mg/mL)^{-1}\ cm^{-1}$. This value has been used during development and will continue to be used to determine the benralizumab protein concentration for commercial use.

b. Mechanism of action

Benralizumab binds to the α subunit of human IL-5R and to FcγRIIIa and mediates ADCC activity. In addition, it blocks the binding of IL-5 to the receptor. IL-5R is expressed on eosinophils and basophils. Interleukin-5 is a hematopoietic cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils. Eosinophilic inflammation is common in asthma, and eosinophils and basophils are thought to play key roles in the pathogenesis and severity of asthma. Increased levels of eosinophils have been found in the airways of patients with chronic bronchial asthma. In vivo, administration of benralizumab leads to depletion of eosinophils. Benralizumab does not elicit CDC activity.

c. Potency Assay

A cell-based bioassay that measures activation of cell signaling as a surrogate measurement of ADCC activity is used to control drug substance (DS), (b) (4) and drug product (DP) potency. A natural killer cell line (NK-92) engineered to express FcγRIIIa and a luciferase reporter gene under control of an NFAT element is used as the effector cells, and a CTLL-2 cell line that expresses IL-5Rα on the surface is used as the target cells. The addition of benralizumab leads to bridging of the target and effector cells, clustering of FcγRIIIa, and the induction of signaling. The amount of luciferase generated is measured using a chemiluminescent substrate and is proportional to ADCC activity. Dose-response curves are analyzed, and the potency of test articles is calculated as a percentage relative to the reference material (RM).

d. Reference material(s)

(b) (4)

e. Critical starting materials or intermediates

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4) The container closure system is suitable for benralizumab, based on stability data and maintenance of closure integrity.

h. Dating period and storage conditions

The dating period for the DS will be (b) (4) months when stored at (b) (4) °C.

C. (b) (4) Drug Product [benralizumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product (b) (4) CQAs that are derived from the (b) (4) (b) (4) drug product manufacturing process (b) (4) and drug product attributes.

Table 3: Drug Product (b) (4) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (DP (b) (4) (contaminant)	Safety (infection) and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination introduced throughout (b) (4) DP manufacturing process or due to failure of container closure integrity	(b) (4)	
Container Closure Integrity (contaminant)	Safety (contamination)	Manufacturing failure or impact of storage conditions		N/A
Endotoxin (contaminant)	Safety and Purity	Contamination introduced throughout (b) (4) DP manufacturing process or due to failure of container closure integrity		N/A
Color and turbidity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A

Particulate Matter (translucent, visible and subvisible) (Product or Process Related Impurities)	Safety/ Immunogenicity	Manufacturing process and CCS	(b) (4)	N/A
Polysorbate 20 concentration	Safety and Efficacy (b) (4)	Manufacturing process		N/A
Deliverable Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Breakloose and Glide Force (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		Based on the extractables studies and stability data, the risk from leachables is low; however, the appropriate studies should be performed to confirm this conclusion. The applicant has confirmed a commitment to preforming the studies, and a PMC will be implemented.

a. Potency and Strength

Benralizumab is supplied at 30 mg/1.0 mL syringe. Potency is defined as the percent activity relative to the current benralizumab RM. The potency assay is the same as described in the DS section of this memo.

b. Summary of Product Design

Benralizumab is supplied as a sterile, single-dose, preservative-free solution for SC injection in a pre-filled syringe. Benralizumab DP is formulated in 9 mM histidine, 11 mM histidine hydrochloride monohydrate, 250 mM α,α-trehalose dehydrate, and 0.006% (w/v) polysorbate 20, pH 6.0. The extractable volume is 1.0 mL.

c. List of Excipients

Excipients include 9 mM histidine, 11 mM histidine hydrochloride monohydrate, 250 mM α,α-trehalose dehydrate, and 0.006% (w/v) polysorbate 20. All excipients are compendial; the histidine hydrochloride monohydrate follows the requirements of Ph.Eur. and JP, because there is no USP monograph/chapter for this material.

d. Reference material(s)

The same reference material is used for DS and DP.

e. Manufacturing process summary

(b) (4)

f. Container closure

(b) (4)

The primary container closure system for benralizumab D (b) (4)

Combined with the current stability and clinical data, the compatibility studies performed for the container closure systems are adequate to support a sufficiently low risk to allow initial marketing; however, a PMC related to container closure leachables will be requested.

The secondary container closure system consists of a tray insert that is placed into a paperboard carton.

g. Dating period and storage conditions

(b) (4)

The dating period for benralizumab DP will be 24 months when stored at 2-8°C.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Store in original carton (b) (4)
- Protect from light (b) (4)
- Do not freeze.
- Do not shake.

APPEARS THIS WAY ON ORIGINAL

F. Establishment Information

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
Site Name	**Address**	**FEI/DUNS Number**	**Responsibility**	**Final Recommendation**
AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC)	633 Research Court Frederick, MD 21703 USA	FEI# 3002617771	Preparation of Future Working Cell Banks; Storage and maintenance of Master and Working Cell Banks; Drug Substance manufacture and Storage; Drug Substance release and stability testing	Acceptable based on PAI of 5/15-23/2017
MedImmune LLC	1 MedImmune Way Gaithersburg, MD 20878 USA	DUNS # 489176682	Preparation of Working Cell Bank Lot 08BG03	No further evaluation necessary per ICH Q7
(b) (4)				No further evaluation necessary per ICH Q7
DRUG PRODUCT				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
(b) (4)			Drug Product manufacture; Release testing for sterility and Endotoxin; Stability testing for sterility; Labeling and packaging	Acceptable based on PAI of (b) (4)
MedImmune UK Ltd.	MedImmune UK Ltd. 6 Renaissance Way Liverpool, L24 9JW United Kingdom	FEI# 3004066112	Release testing	Acceptable based on PAI of 2/13-17/2017
AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC)	633 Research Court Frederick, MD 21703 USA	FEI# 3002617771	Release testing	Acceptable based on PAI of 5/15-23/2017

G. Facilities

The BLA proposes commercial manufacture of benralizumab DS and DP at AstraZeneca Pharmaceutical LP, Frederick, MD, USA (FEI 3002617771) (b) (4) DP release testing will also occur at MedImmune UK Ltd., Liverpool, UK (FEI 3004066112).

A Pre-license Inspection was performed at AstraZeneca Pharmaceutical LP, 5/15-23/2017. A three item Form FDA 483 was issued. The initial field recommendation for the firm is VAI and approval of BLA 761070/0. An OPF/DIA review of the inspection deemed the firm's 483 response adequate and recommended approval of the facility in regard to BLA 761070 under the CBI profile. The inspection was finalized as VAI. The compliance status of this benralizumab DS manufacturing facility is acceptable.

A Pre-license Inspection was performed at MedImmune UK Ltd., 2/13-17/2017. The inspection was classified as NAI. The compliance status of this benralizumab DP testing facility is acceptable.

A Pre-license Inspection was also performed at (b) (4) A four-item FDA Form 483 was issued for: 1) inadequate process simulations (b) (4) 2) inadequate QC sample controls; 3) inadequate investigation of particles (b) (4) and 4) inadequate computerized system validation. Withhold approval of BLA 761070 was recommended by the inspection team. An OPF/DIA review of the PLI deemed the firm's response to FDA Form 483 adequate and recommended approval of the individual facility for (b) (4) in regard to BLA 761070 under the SVS profile. The inspection was finalized as VAI. The compliance status of this benralizumab DP manufacturing facility is acceptable.

H. Lifecycle Knowledge Management

a. Drug Substance
   i. Protocols approved: At-scale validation of (b) (4) annual stability and protocol for extension of expiry, new WCB, new RS, (b) (4)
   ii. Outstanding review issues/residual risk: See risk evaluation above
   iii. Future inspection points to consider:
      1. Implementation of appropriate harvest operation discharge interval
      2. Review of updated potency assay SOPs to ensure independent assay control is required and of trending of RS and assay control EC50 results
      3. Review of system suitability requirements for the cIEF assay

b. Drug Product
   i. Protocols approved: Annual stability and stability extensions for (b) (4) Drug Product, (b) (4)
   ii. Outstanding review issues/residual risk: See PMC
   iii. Future inspection points to consider: None

Zhihao Peter Qiu

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Date: 10/04/2017 09:01:05AM
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Patricia Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 10/04/2017 12:14:50PM
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Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 10/04/2017 08:56:02AM
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Kathleen Clouse Strebel

Digitally signed by Kathleen Clouse Strebel
Date: 10/05/2017 03:28:46PM
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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	October 4, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Jennifer Swisher, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761070
Product:	Fasenra (benralizumab)
Applicant:	AstraZeneca AB
Submission Date(s):	November 16, 2016, August 11, 207, September 5, 2017, and September 27, 2017

I) RECOMMENDATION

The labels and labeling for Fasenra (benralizumab) injection, 30 mg/mL single-dose prefilled syringe for subcutaneous use submitted on August 11, 2017 (container labels and carton labeling), September 5, 2017 (lidding labeling), and September 27, 2017 (prescribing information) are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761070 for Fasenra (benralizumab) on November 16, 2016.

Table 1: Proposed Product Characteristics of benralizumab.

Proprietary Name:	Fasenra
Nonproprietary Name:	Benralizumab
Dosage Form:	injection
Strength and Container-Closure:	30 mg/mL single dose prefilled syringe
Route of Administration:	subcutaneous
Storage and Handling:	refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light
Indication:	as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
Dose and Frequency:	30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter

MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (N/A)
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

III) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

IV) CONCLUSION

The prescribing information, patient labeling, container labels, and carton labeling for Fasenra (benralizumab) injection 30 mg/mL single-dose prefilled syringe were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100, United States Pharmacopeia (USP) standards, and best labeling practices. The labels and labeling submitted on August 11, 2017 (container labels and carton labeling), September 5, 2017 (lidding labeling), and September 27, 2017 (prescribing information) are acceptable (see Appendix D) from a quality perspective.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B: Other

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	considered a partial label
Manufacturer name, address, and license number 21 CFR 610.60			x	considered a partial label
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			x	considered a partial label
Expiration date 21 CFR 610.60 21 CFR 201.17			x	considered a partial label
Multiple dose containers (recommended individual dose) 21 CFR 610.60			x	single dose prefilled syringe
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	x			Unbold and reduce prominence of "Rx Only" to allow for prominence of other critical information on the Principal display panel (PDP). *Applicant revised as requested*
Medication Guide 21 CFR 610.60			x	

[1] Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 208.24				
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10		x		Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.60(a)(2). Revise from "AstraZeneca" to read "AstraZeneca AB". *Applicant revised as requested*
No container label 21 CFR 610.60			x	
Ferrule and cap overseal			x	PFS
Visual inspection 21 CFR 610.60			x	
NDC numbers 21 CFR 201.2 21 CFR 207.35			x	Not required for partial labels per 21 CFR 610.60(c).
Route of administration 21 CFR 201.5 21 CFR 201.100			x	container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).
Preparation instructions 21 CFR 201.5			x	considered a partial label
Package type term 21 CFR 201.5			x	considered a partial label
Drugs Misleading statements 21 CFR 201.6	x			
Strength 21 CFR 201.10 21CFR 201.100	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Bar code label requirements 21 CFR 201.25	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21CFR 610.67				
Net quantity 21 CFR 201.51			x	considered a partial label
Usual dosage statement 21 CFR 201.55 21 CFR 201.100			x	container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).
Inactive ingredients 21 CFR 201.100			x	container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).
Storage requirements			x	considered a partial label
Dispensing container 21 CFR 201.100			x	

Package Label[5] Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			
Manufacturer name, address, and license number 21 CFR 610.61				On the lidding and the carton labeling, ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.61. Revise from (b) (4) to read "Manufactured by: AstraZeneca AB" Sodertalje, Stockholm County Sweden SE-15185 US License No. XXXX" The applicant may include the distributor name and address since they have fulfilled 21 CFR 610.61(b). *Applicant's revision is acceptable* Remove the word (b) (4) from the US license No. statement. *The Applicant revised as requested.*

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Lot number or other lot identification 21 CFR 610.61	x			
Expiration date 21 CFR 610.61 21 CFR 201.17	x			
Preservative 21 CFR 610.61		x		Ensure "No preservative" appears on the lidding labeling per 21 CFR 610.61 (e). *The Applicant responded that they consider the lidding to be a partial label and that this not be added in order to maintain white space.* *The Agency does not consider the lidding labeling a partial label since the partial label regulation pertains to container labels [see 21 CFR 610.60 (c)]. "No preservative" is required information per 21 CFR 610.61 (e). To accommodate the addition of this information, consider locating the statement to appear on the line after "Do Not Shake or Freeze."* *The Applicant revised as requested.*
Number of containers 21 CFR 610.61			x	
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
Storage temperature 21 CFR 610.61		x		On the lidding and the carton labeling, revise the storage statement from (b) (4) to read "Store the prefilled syringe refrigerated at 2ºC - 8ºC (36ºF - 46ºF) in original carton to protect from light. Do not shake or freeze the syringe." *Applicant revised as requested*
Handling: "Shake Well", "Do not Freeze" or equivalent 21 CFR 610.61	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Multiple dose containers (recommended individual dose) 21 CFR 610.61			x	single dose
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
Known sensitizing substances 21CFR 610.61			x	
Antibiotics added during manufacturing 21 CFR 610.61			x	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100		x		Revise the inactive ingredients list from (b) (4) to read "Contents: One 1-mL single-dose prefilled syringe that delivers 30 mg benralizumab, L-histidine… and Water for Injection, USP." Ensure that the inactive ingredients appear in alphabetical order per USP <1091> Labeling of Inactive Ingredients. *The Applicant revised as requested* Add the list of inactive ingredients to the lidding labeling. To accommodate this addition, remove the trademark statement, as the trademark statement is not required information per 21 CFR 201.15. *The Applicant responded that they consider the lidding to be a partial label and that this not be added in order to maintain white space.* *The Agency does not consider the lidding labeling a partial label. However, we agree with the considerations for space and this information will appear on the carton and in prescribing information.*
Adjuvant, if present 21 CFR 610.61			x	
Source of the product			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.61				
Identity of each microorganism used in manufacturing 21 CFR 610.61			x	See listing in PI
Minimum potency of product 21 CFR 610.61		x		On the lidding, add the words "No U.S. standard of potency" per 21CFR 610.61 (r) *The Applicant responded that they consider the lidding to be a partial label and that this not be added in order to maintain white space.* *The Agency does not consider the lidding labeling a partial label. "No U.S. standard of potency" statement is required information per 21 CFR 610.61 (r). This can be added as follows:* *"Do not shake or freeze the syringe.* *No Preservative. No U.S. Standard of Potency"* *The Applicant revised as requested.*
Rx only 21CFR 610.61 21 CFR 201.100	x			
Divided manufacturing 21 CFR 610.63			x	
Distributor 21 CFR 610.64			x	
Bar code 21 CFR 610.67 21 CFR 201.25	x			
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26			x	
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Preparation	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
instructions 21 CFR 201.5				
Package type term 21 CFR 201.5		x		Relocate and revise the discard statement to appear adjacent to the package type term as follows: "1 single-dose prefilled syringe. Discard unused portion." *Applicant revised as requested*
Drugs Misleading statements 21 CFR 201.6			x	
Drugs Prominence of required label statements 21 CFR 201.15		x		see inactive ingredient assessment above
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100		x		On the carton labeling, revise the usual dose statement from (b) (4) to read "Usual Dosage: See prescribing information" per 21 CFR 201.55. *Applicant revise as requested*
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION	x			

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.57(a)(7)				
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	x			
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	x			
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Added identifying characteristics per 21 CFR 201.57(c)(4) TRADENAME is a clear to opalescent, colorless to slightly yellow solution and may contain a few translucent or white to off-white particles *Applicant revised as requested*
6.2 IMMUNOGENICITY		x		Relocated the last paragraph to appear at the beginning of this section and revised the language for this standard statement based on our current labeling *Applicant revised as requested*
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Deleted (b) (4) from first paragraph since this paragraph discusses the drug substance *Applicant revised as requested* Added the dosage form per 21 CFR 201.57(c)(12) *Applicant revised as requested* Per OND best labeling practices revise the list of all inactive ingredients in alphabetical order (see USP Chapter <1091>) followed by their quantitative information using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection. *Applicant revised as requested*
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		Added dosage form per 21 CFR 201.57(c)(17) to first paragraph *Applicant revised as requested* Revised the strength from (b) (4) to "30 mg/mL" as appropriate for this dosage form.

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				Applicant revised as requested Revised the storage statement for readability *Applicant revised as requested*
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64		x		Add the licensed manufacturer per 21 CFR 610.61(b) *Applicant revised as requested* The applicant may include the distributor name and address since they have fulfilled 21 CFR 610.61(b). We revised the qualifying phrase per 21 CFR 610.64 "Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850" *Applicant revised as requested*
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
TITLE (NAMES AND DOSAGE FORM)	x			
STORAGE AND HANDLING			x	HCP administered
INGREDIENTS	x			
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64		x		Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.61. Revise from (b) (4) to read "Manufactured by: AstraZeneca AB Sodertalje, Stockholm County Sweden SE-15185 US License No. XXXX" *Applicant revised as requested* The applicant may include the distributor name and address since they have fulfilled 21 CFR 610.61(b). We revised the qualifying phrase per 21 CFR 610.64 "Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850" *Applicant revised as requested*

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

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Jennifer Swisher

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BLA STN 761070

Fasenra (benralizumab)

AstraZeneca

Jennifer Swisher, Ph.D., Product Quality Reviewer
Sarah Kennett, Ph.D., Review Chief
Kathleen Clouse, Ph.D., Division Director
Division of Biotechnology Review and Research I
Office of Biotechnology Products

OBP CMC Data Sheet

1. **BLA#:** STN 761070

2. **REVIEW DATE:** July 13, 2017

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Sofia Chaudhry and Lydia Gilbert McLain (TL)
Pharm/Tox: Timothy Robison and Carol Galvis (TL)
Product Quality Team: Jennifer Swisher and Sarah Kennett (TL)
BMT or Facilities: Maria Jose Lopez-Barragan and Maria Reyes Candau-Chacon (TL), Candace Gomez-Broughton and Dupeh Palmer (TL), Zhong Li and Peter Qiu (TL)
Clinical Pharmacology: Suryanarayana Sista and Anshu Marathe (TL)
Statistics: Yu Wang and Gregory Levin (TL)
OBP Labeling: Vicky Borders-Hemphill
OPRO RBPM: Kelly Ballard
OND RPM: Colette Jackson

4. **MAJOR 21st Century Review DEADLINES**
Filing Meeting: January 11, 2017
Mid-Cycle Meeting: April 27, 2017
Primary Review Due: July 16, 2017
Wrap-Up Meeting: September 29, 2017
PDUFA Action Date: November 16, 2017

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

Communication/Document	Date
Filing Letter	January 27, 2017
Information Request #1	March 21, 2017
Information Request #2	March 24, 2017
Information Request #3	May 16, 2017
Information Request #4	June 14, 2017
Information Request #5	June 21, 2017
Information Request #6	July 13, 2017
Information Request #7	August 18, 2017
Information Request #8	September 14, 2017

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

Submission	Date Received	Review Completed
761070/1 Original BLA Submission	11/16/2016	Yes
761070/4 (Response to filing letter)	02/01/2017	Yes
761070/11 (Response to IRs #1 and #2)	04/04/2017	Yes
761070/16 (Response to IR #3)	05/25/2017	Yes
761070/19 (Response to IR #4)	06/30/2017	Yes
761070/20 (Response to IRs #4 and #5)	7/10/2017	Yes
761070/26 (Response to IR #6)	08/11/2017	Yes
761070/29 (Response to IRs #6 and #7)	09/01/2017	Yes
761070/32 (Response to IRs #8)	9/25/2017	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Fasenra
   b. Trade Name: Fasenra
   c. Non-Proprietary/USAN: benralizumab
   d. CAS Registration Number: 1044511-01-4
   e. Common name: benralizumab
   f. INN Name: benralizumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI Q01344 (IL5RA_HUMAN) [MEDI563]
   i. Other Names: MEDI-563

8. **PHARMACOLOGICAL CATEGORY:** Interleukin-5 receptor alpha-directed cytolytic monoclonal antibody

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**
   i. **The concentration/strength of the Drug Product:** 30 mg/mL solution in a single-dose pre-filled syringe
   ii. **Type of potency assay:** A cell-based Antibody Dependent Cellular Cytotoxicity (ADCC) assay is utilized to determine the potency of benralizumab. ADCC activity is the main MOA for this product. Potency is reported as a percent of reference standard activity.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	Reviewed[1]
			Yes	Adequate information provided in the BLA for its intended use
			Yes	Type III; Adequate information provided in the BLA for its intended use
			Yes	Type III; Adequate information provided in the BLA for its intended use
			Yes	Type III; Adequate information provided in the BLA for its intended use

1 -Only select items were reviewed when necessary for review of a particular manufacturing step.

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the biologics drug substance [redacted] (b) (4) manufacturing facility was conducted at AstraZeneca Frederick Manufacturing Center (FMC) in Frederick, Maryland (FEI 300261771) on May 15-19, 2017 by ORA reviewers Arie Menachem and Anastasia Shields and OBP DBRR I reviewer Jennifer Swisher. The site is responsible for the manufacture of DS, [redacted] (b) (4) and DP release and stability testing. Four 483 observations were issued at the end of the inspection. The recommendation of the inspection team was VAI.

A pre-licensure inspection (PLI) was also performed at [redacted] (b) (4) the drug product manufacturing facility, on [redacted] (b) (4) by DMA reviewer Maria Cruz-Fisher, DIA reviewer Wayne Siefert, and ORA Consumer Safety Officer Diane Raccasi. A four item 483 was issued and the initial recommendation of the inspection team was to withhold approval of the BLA. However, an OPF/DIA review of the firm's response to the 483 found it adequate and the inspection was finalized as VAI.

14. CONSULTS REQUESTED BY OBP

A CDRH consult was requested by OBP.

15. QUALITY BY DESIGN ELEMENTS

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

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Kathleen Clouse, Ph.D. Division Director Office of Biotechnology Products Division of Biotechnology Products Review and Research 1	See Panorama
Jennifer Swisher, Ph.D. Team Leader Office of Biotechnology Products Division of Biotechnology Products Review and Research 1	See Panorama

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

Initially, from a microbiology perspective, deficiencies in the BLA had not been adequately addressed, and the data and information reviewed by the Office of Biotechnology Products were not yet fully sufficient to support approval. However, the deficiencies and other issues have been resolved. The data submitted in this Biologics License Application support the conclusion that the manufacture of Fasenra (benralizumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Fasenra (benralizumab) be approved for human use (under conditions specified in the package insert).

II. List Of Deficiencies To Be Communicated

N/A

III. List Of Post-Marketing Commitments/Requirements

To perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

IV. Review Of Common Technical Document-Quality Module 1

Environmental Assessment or Claim Of Categorical Exclusion

A claim for categorical exclusion under 21 CFR 25.31 (e) was made. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review is being performed under separate cover by Vicky Borders-Hemphill.

VI. Review Of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided for benralizumab DS (Section 3.2.S), (b) (4) DP (Section 3.2.P), the adventitious agents safety evaluation (3.2.A) and the method validation package and batch records (3.2.R).

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

A review of the immunogenicity assays is provided at the end of the primary review document. The immunogenicity evaluation is composed of four assays: anti-drug antibody (ADA) screening, ADA confirmation, neutralizing ADA screening, and neutralizing ADA confirmation.

TABLE OF CONTENTS

APPEARS THIS WAY ON ORIGINAL

DRUG SUBSTANCE AND DRUG PRODUCT

3.2.S DRUG SUBSTANCE

3.2.S.1.2 Nomenclature

- Chemical Abstract Service (CAS) name: Immunoglobulin G1, anti-(human interleukin 5 receptor α-chain)(human-mouse monoclonal MEDI-563 heavy chain), disulfide with human-mouse monoclonal MEDI-563 α-chain, dimer
- CAS Registry Number: 1044511-01-4
- Generic Name (USAN, INN): Benralizumab
- Trade Name: Pending
- Laboratory Codes:
  - MEDI-563
  - 01P003 (at the MedImmune Frederick Manufacturing Center (FMC));
  - (b) (4)
  - BIW-8405 (the initial product designation at Biowa/Kyowa Hakko Kirin)

3.2.S.1.2 Structure

Benralizumab is a recombinant humanized afucosylated IgG1k monoclonal antibody against the interleukin (IL)-5 receptor. It is comprised of two heavy chains (~49.4 kDa each) and two light chains (~23.5 kDa each). It has primarily N-linked biantennary complex oligosaccharides (without fucose) attached to each heavy chain at Asn-301; the average size of each oligosaccharide moiety is 1.5 kDa. The sequences of the light and heavy chains are:

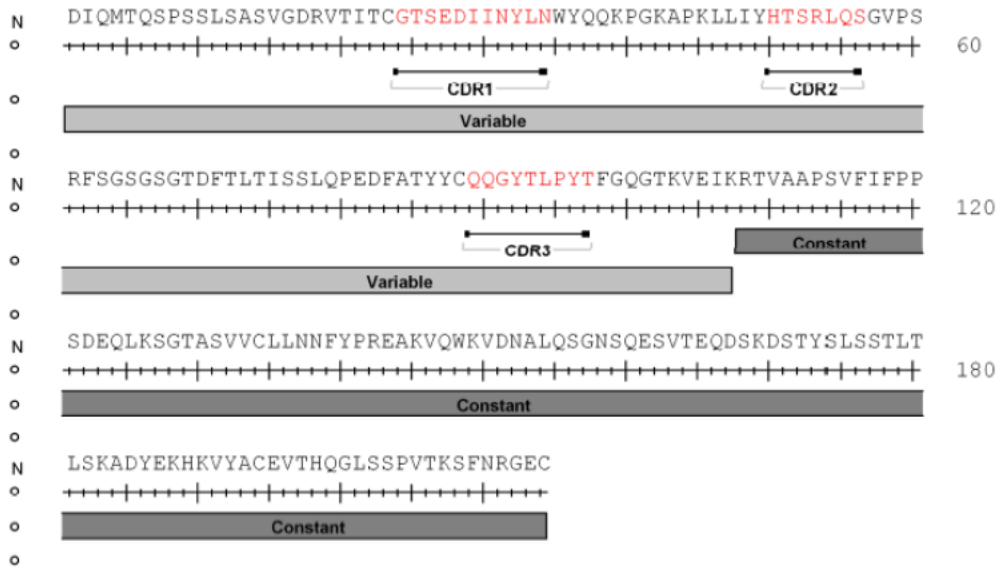

Figure S.1.2-1 Nucleotide and Deduced Amino Acid Sequence of Benralizumab V_L Region

CDR sequences, variable and constant domains are labelled. Murine residues are indicated in red.

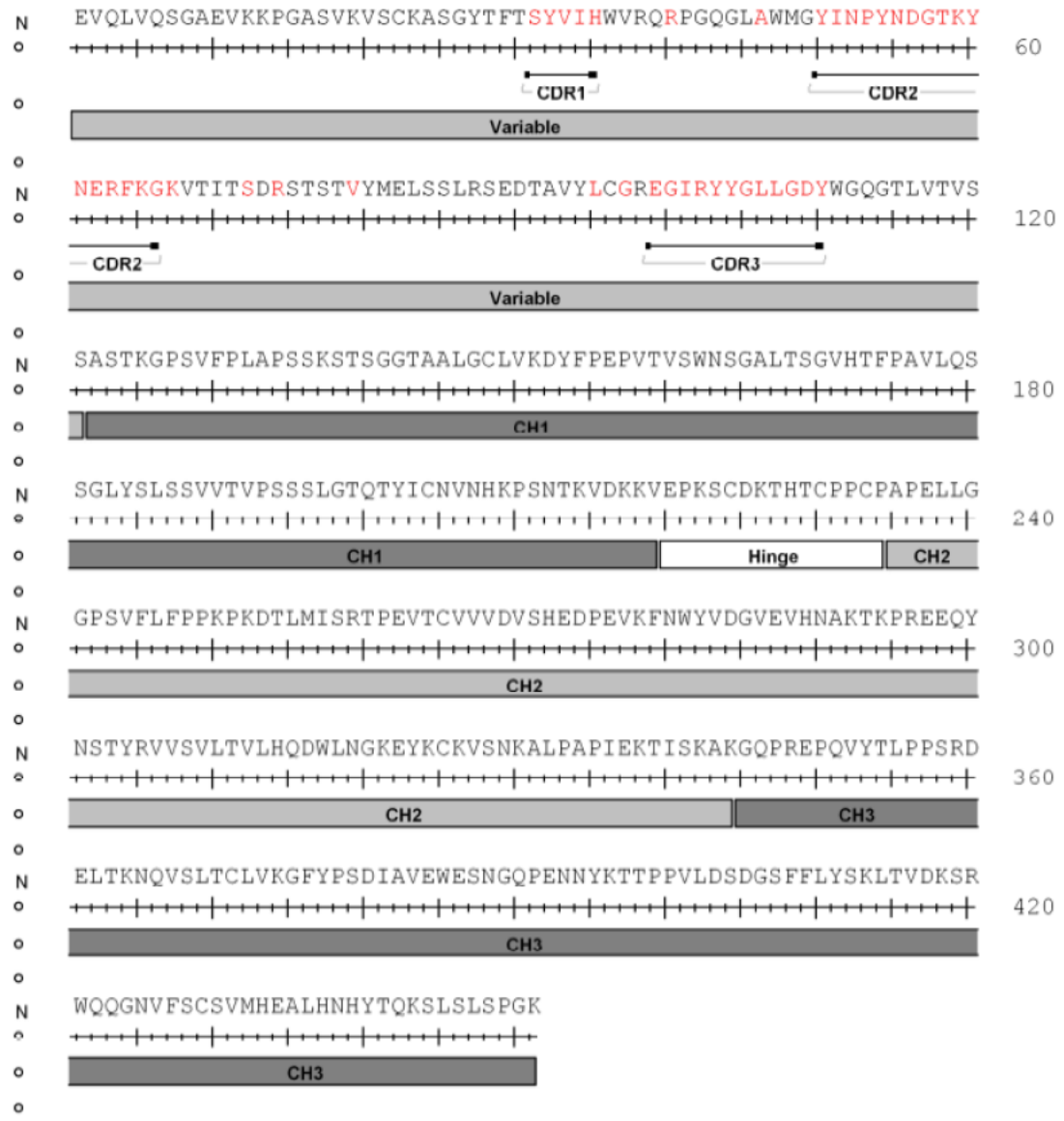

Figure S.1.2-2 Nucleotide and Deduced Amino Acid Sequence of Benralizumab V_H Region

CDR sequences, variable and constant domains are labelled. Murine residues are indicated in red.

3.2.S.1.3 General Properties

Benralizumab is a humanized, afucosylated IgG1k monoclonal antibody targeted against the α chain of the IL-5 receptor, a glycoprotein expressed on B-cells and granulocytes (eosinophils, basophils, mast cells, and to a lesser degree, neutrophils). The major isoforms of benralizumab have isoelectric points between 8.4 and 8.9 and an experimentally determined extinction coefficient of 1.43 $(mg/mL)^{-1}$ cm^{-1}, which has been used throughout development. The removal of fucose from the Fc glycan improves binding to FcγRIIIα, imparting an enhanced capacity to carry out antibody dependent cellular cytotoxicity (ADCC) against IL-5Rα expressing cells, such as eosinophils and basophils.

Reviewer comment: *While non-clinical data suggest that benralizumab can affect ADCC against eosinophils and basophils, the mechanism of action may involve a combination of IL-5Rα neutralization and direct killing of IL-5Rα -bearing cells. In nonclinical studies, the antibody representing the fucosylated parent of benralizumab is roughly 1000x less efficacious at killing eosinophils by ADCC than benralizumab (Kolbeck et al. (2010) J. Allergy Clin Immunol 125:1344–53). In addition, because IL-5Rα is a cell surface protein, benralizumab may exert effects different than those displayed by the IL-5 neutralizing antibodies mepolizumab and reslizumab that result in dramatically elevated IL-5 levels (if not higher IL-5 bioactivity) in mepolizumab and reslizumab treated patients.*

When benralizumab is bound to the IL-5Rα on eosinophils, it can either block IL-5 binding and signaling or recruit NK cells via an FcγRIIIα-mediated ADCC pathway, thereby eliciting selective killing of eosinophils and other IL-5Rα-bearing cells. Because it contains a human IgG1 Fc region, it could also enable deletion of IL-5Rα-bearing cells by other FcγR-bearing effector cells (such as neutrophils and macrophages, and possibly eosinophils themselves). Benralizumab has demonstrated potency in vivo based on reduction of symptoms as well as deletion of eosinophils in a cynomolgus monkey asthma model and in vitro by antibody-dependent cellular cytotoxicity (ADCC) assays with primary human eosinophils, basophils, and transfected IL-5Rα-expressing target cells. In vitro characterization suggests that benralizumab is not capable of eliciting complement-dependent cytotoxicity (CDC). The potency assay proposed for assessing the biological activity of benralizumab for release and stability measures ADCC activity using an NK cell line engineered to express human FcγRIIIα and a luciferase reporter gene as the effector cell and a CTLL-2 cell line engineered to express human IL-5Rα as the target cell. See discussion in the relevant sections below.

Reviewer comment: *Nonclinical data support these mechanisms (Module 4). Benralizumab was demonstrated to bind specifically to human peripheral blood-derived eosinophils, inhibit growth of an IL-5Rα-expressing cell line in response to IL-5, and induce ADCC of an IL-5Rα-transfected EL4 cell line using the NK-92 effector cell line (which expresses only the high affinity variant of FcγRIIIα with valine at position 158) and of human eosinophils using PBMC as effector cells. This latter study also demonstrated that ADCC of human eosinophils is carried out without causing eosinophil degranulation into the media. The Kolbeck publication also shows depletion of eosinophil precursors in the bone marrow, which is novel for an IL-5 pathway-targeted antibody therapy. It is also possible that benralizumab can elicit antibody-dependent cellular phagocytosis (ADCP) through macrophages and may invoke deletional mechanisms through neutrophil and eosinophil Fcγ receptors as well.*

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The benralizumab manufacturing sites and their responsibilities are listed in the following table.

Table S.2.1-1 Drug Substance Manufacturing and Testing Sites

Name and Address	Facility Identifier	Responsibilities
(b) (4)		
MedImmune LLC 1 MedImmune Way Gaithersburg, MD 20878 USA	DUNS 489176682	• Preparation of Working Cell Bank Lot 08BG03
MedImmune LLC Frederick Manufacturing Center (FMC) 633 Research Court Frederick, Maryland 21703 USA	FEI: 3002617771 DUNS 968459953	• Preparation of Future Working Cell Banks • Storage and maintenance of Master and Working Cell Banks • Drug Substance manufacture and storage • Drug Substance release and stability testing

DUNS = Data Universal Numbering System Number; FEI = Facility Establishment Idenitifier

Facility and equipment information for MedImmune LLC, Frederick, MD is contained in DMF (b) (4)

3.2.S.2.2. Description of Manufacturing Process and Process Controls

(b) (4)

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3.2.P Drug Product

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

DP is supplied as a sterile, single-dose, 1.0 mL of 30 mg/mL benralizumab formulated in 9 mM histidine, 11 mM histidine hydrochloride monohydrate, 250 mM α,α-trehalose dehydrate, and 0.006% (w/v) polysorbate 20, pH 6.0 in an accessorized prefilled syringe (APFS). The quantitative and qualitative composition of benralizumab DP is presented in the table below.

Table P.1-1 Composition of the Drug Product

Ingredient	Concentration	Unit Formula per 30 mg syringe	Purpose	Quality Standard
Active Ingredient				
Benralizumab	30 mg/mL	30 mg	Active	In-house Reference Standard
Excipients				
L-Histidine	9 mM	1.4 mg	(b) (4)	USP/NF; Ph. Eur.; JP
L-Histidine hydrochloride monohydrate	11 mM	2.3 mg		Ph. Eur.; JP
α,α-trehalose dihydrate	0.25 M	95 mg		USP/NF; Ph. Eur.; JP
Polysorbate 20 (b) (4)	0.006% w/v	0.06 mg		USP/NF; Ph. Eur., JP
Water for Injection	Not applicable	Approximately (b) (4) mg		USP/NF; Ph. Eur., JP

JP = Japanese Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; USP/NF = United States Pharmacopeia/ National Formulary

Reviewer Comment: *There is no USP/NF chapter/monograph for L-histidine hydrochloride monohydrate; therefore, the use of Ph.Eur./JP grade material is appropriate.*

The container closure for the DP is a prefilled syringe (b) (4)

(b) (4)

3.2.P.2. Pharmaceutical Development

3.2.P.2.1 Components of Drug Product

(b) (4)

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(b) (4)

Drug Product Stability

The benralizumab DP stability program is conducted using the commercial 1 mL prefilled syringe (b) (4) (PFS (b) (4) as the primary container closure, and all "primary" and "commitment" materials in the commercial formulation. Stability studies include the long-term storage condition of 2-8°C, an accelerated condition of 23-27°C/55-65% relative humidity (RH), and a stressed condition of 38-42°C/70-80% RH. The tests and timepoints are presented in Tables P.8.1.2.2-2 and P.8.1.2.2-3, and the acceptance criteria are presented in Section 3.2.P.8.3. The data points currently available for the real-time studies include 12 months (updated to 18 months) for the three Process 3 Commercial validation ("commitment") lots (020F15, 021F15, and 004K15) and 36 months for five Process 3 Clinical lots (026A13, 002C14 and 001L14 at 30 mg/mL, 004I12 a (b) (4) mg/mL, 005I12 at (b) (4) mg/m; referred to by the sponsor as the primary lots, and referred to in the review as supporting lots). All accelerated and stressed studies are complete for the planned 6 months under accelerated conditions and 3 months under stressed conditions.

(b) (4)

(b) (4)

Reviewer comment: *The sponsor proposed a* (b) (4) *month shelf-life but provided only 12 months of data for the lots manufactured by the commercial process. Therefore, they were requested to update the BLA with all available stability data, and 18 months of data were provided. The supporting lots were manufactured using clinical process DS and the clinical DP manufacturing process. For commercial DP manufacturing, additional steps are included, and the hold periods allowed are quite long. In addition, the comparability study was performed with clinical material in the finished presentation but commercial material in the unfinished presentation, providing the possibility that not all potential difference was captured. While these steps and holds appear to have limited impact on product quality, there are clear changes in product quality attributes on stability, and actual real-time stability data are needed to fully support the expiry period. However, the clinical process materials appear sufficiently representative to provide some support for setting an initial expiry period that is extended beyond the 18 months for which real time commercial data are currently available. Therefore, the sponsor was requested to change the expiry period to 24 months and was advised that the expiry can be extended under a protocol if the results are acceptable when the next timepoint is reached. The sponsor updated the expiry to 24 months and updated Section 3.2.P.8.2 to state that shelf life extension to* (b) (4) *months will be based on real time data.*

The stressed stability data show that DP storage at temperatures (b) (4)

The review of container closure integrity results are deferred to DMA and the review of breakloose/extrusion force and rigid needle shield removal force results appear acceptable but are deferred to CDRH.

Photostability Studies

Photostability studies were performed in order to assess how light exposure might impact the packaged product. The studies were conducted using benralizumab exposed to light according to ICH Q1B option 2. DP samples stored in the commercial marketing pack (boxed PFS) or in a dark control (commercial packaging wrapped in foil) were compared after treatment with ≥1.2 million lux-hours at ≥200 watt hours/square meter

Reviewer Comment: *As would be expected, light exposure did not impact the quality of DP samples in their secondary packaging. Under routine manufacturing conditions, there was no significant impact of light on aggregates or acidic variants (see DP development). Under ICH CWL conditions, there were increases in oxidation; however, the increases did not appear to impact potency and may have had a minimal impact on FcRn binding. There was clear impact to FcRn binding only at the levels of oxidation seen under ICH CWL plus UV light conditions. Because limited impact to potency or FcRn binding was seen, it can be assumed that exposure to light did not lead to significant fragmentation. Therefore, under standard conditions or practical worst-case conditions, exposure to light should not significantly impact benralizumab DP.*

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Jennifer Swisher

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Kathleen Clouse Strebel

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Date: 10/02/2017 12:59:50PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: September 19, 2017
To: Administrative File, **STN 761070/0**
From: Zhong Li, Ph.D., Chemist, CDER/OPQ/OPF/DIA/Branch 1
Endorsement: Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA/ Branch 1
Subject: **Original BLA Facility Review; Amendment 1**
US License: Not available
Applicant: **AstraZeneca AB**
Mfg. Facilities: Drug Substance: ***AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center***, Frederick, MD, USA FEI 3002617771
Drug Product: (b) (4)

Drug Name/Dosage Form: Benralizumab / Solution for Subcutaneous Injection
Strength/Potency: 30 mg/mL
Indication: as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older
Goal Date: 11/16/2017

RECOMMENDATION

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

Background

This document is an amendment to the original Facility Review for BLA 761070/0 that was filed in the Panorama review platform on July 11, 2017.

In the 7/11/2017 Facility Review, the drug substance facility assessment was pending for AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771). A pre-approval inspection was conducted at the facility from 5/15-23/2017, with an OPF/DIA compliance review pending as of 7/10/2017. All other proposed manufacturing and testing sites were recommended for approval from a facilities assessment standpoint in the review.

The 5/15-23/2017 inspection report and the applicable firm's responses have since been available to and reviewed by OPF/DIA. This amendment provides an updated and final assessment of the pre-approval inspection of the DS manufactuering facility as well as a final Overall Manufactuering

Inspection Recommendation. All other manfactuering facilities evaluation was documented in the 7/11/2017 Facility Review and since it was complete, is not reproduced here.

ASSESSMENT

DRUG SUBSTANCE FACILITY

- **3.2.S.2.1 DS Manufacturer**

  The site proposed for commercial manufacturing and testing of Benralizumab DS is presented below in **Table 1**.

  TABLE 1. Proposed Site for Benralizumab DS Manufacturing and Testing Operations

Site Name	Address	FEI Number	Responsibilities
AstraZeneca Pharmaceutical LP, Frederick Manufacturing Center (Formerly known as MedImmune LLC, FMC)	633 Research Court Frederick, Maryland 21703, USA	3002617771	Manufacturing of drug substance; Release testing, Stability testing; Working Cell bank manufacture and storage

- **Current Pre-approval Inspection Decision**

  AstraZeneca Pharmaceutical LP, FMC (FEI 3002617771)

  A pre-approval inspection of AstraZeneca Pharmaceutical LP in Frederick, MD, USA was completed in support of BLA 761070/0 for Benralizumab. The inspection occurred from ***5/15-23/2017*** and was conducted in accordance with CP 7346.832, CP 7356.002M, and PAC 46832M. The current inspection included the firm's Quality, Production, Materials, Facilities and Equipment, and Laboratory Controls System in order to assess the firm's readiness for manufacturing, conformance to application, and data integrity audit. A 4-item FDA-483 was issued at the conclusion of the inspection, citing *inadequate controls to prevent microbial contaminations; inadequate WFI sampling procedure; inadequate training, and inadequate adverse drug experiences reporting*. The inspection was initially classified **VAI**; and approval of BLA 761070 was recommended by the inspection team. The firm's responses to FDA-483 observations have been reviewed by OPF/DIA and deemed adequate. OPF/DIA concurs with the VAI recommendation and recommends approval for BLA 761070 (CMS WA #163807).

Reviewer Comment 1: *The proposed DS manufacturing facility, AstraZeneca Pharmaceutical LP, Frederick Manufacturing Center (FMC) (FEI 3002617771), is acceptable from a facility inspectional assessment standpoint.*

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for AstraZeneca Pharmaceutical LP, FMC (FEI 3002617771) proposed for commercial Benralizumab DS manufacture. All proposed DS and DP manufacturing and testing facilities are acceptable based on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility review perspective..

Zhong Li

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Zhihao Peter Qiu

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Date: 9/19/2017 04:25:02PM
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

Date: June 21, 2017
STN: 761070/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Dupeh Palmer, Ph.D. Quality Assessment Lead CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologics License Application
Applicant: AstraZeneca AB
Facilities: (b) (4)
Product: FASENRA™ (benralizumab)
Dosage: solution for subcutaneous injection (30 mg/mL)
Indication: Add-on maintenance treatment for patients with severe asthma
Action Date: November 16, 2017

Recommendation:
The BLA is for approval from a microbiological product quality perspective.

Introduction
AstraZeneca AB has submitted an original Biologics License Application (BLA 761070) for the approval of benralizumab. Benralizumab is a monoclonal antibody produced in Chinese hamster ovary (CHO) cells that is selective for interleukin 5Rα. The benralizumab drug product (DP) is composed of 30 mg in 1.0 mL solution with a prefilled syringe presentation.

This review covers the drug product manufacturing process. The drug substance portion is covered in a separate review completed by Maria Lopez-Barragan.

Assessment
P Drug Product
P.1 Description and Composition of the Drug Product
The benralizumab DP consists of 30 mg/mL of benralizumab in 20 mM histidine/histidine-HCL, 0.25 M trehalose dehydrate, 0.006% w/v polysorbate 20, pH 6.0. The DP is presented in an accessorized prefilled syringe (APFS). (b) (4)

The accessories do not contact the DP solution and are not part of the fluid path of the delivery system.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes
The benralizumab DP is a preservative-free sterile liquid (b) (4) manufactured and filled into syringes. Container closure integrity was evaluated as part of the validation studies which are discussed in Sections P.3.5.2, P.3.5.6, and P.3.5.7.

P.3 Manufacture
P.3.1 Manufacturer(s)
The facilities in which the benralizumab DP is manufactured and tested are listed in the following table.

Facility	FEI #	Responsibilities
		(b) (4)
MedImmune LLC Frederick Manufacturing Center, Frederick, MD	3002617771	(b) (4) release and stability testing, Quality Assurance release
MedImmune UK Ltd. Liverpool, United Kingdom	3004066112	Release Testing

Reviewer comment: The applicant has submitted Letters of Authorization to access Drug Master Files for both the (b) (4) *and MedImmune LLC, FMC (DMF* (b) (4) ***. DMF*** (b) (4) ***was reviewed by Dupeh Palmer and was adequate.***

P.3.2 Batch Formula

Batch size range for benralizumab DP is (b) (4) to (b) (4) syringes. Typical batch size is (b) (4) syringes. The batch formula for benralizumab is summarized in Table P.3.2-1 from the submission and provided below.

Component	Amount per Batch	Quality Standard
Benralizumab	(b) (4) kg	In-house Reference Standard
L-Histidine	g	USP/NF; Ph. Eur.; JP
L-Histidine hydrochloride monohydrate	g	Ph. Eur.; JP
α,α-trehalose dihydrate	kg	USP/NF; Ph. Eur.; JP
Polysorbate 20	g	USP/NF; Ph. Eur., JP
Water for Injection	Approximately (b) (4) kg	USP/NF; Ph. Eur., JP

JP = Japanese Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; USP/NF = United States Pharmacopeia/ National Formulary

P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

P.8 Stability

P.8.1 Stability Summary and Conclusion

Benralizumab has a proposed shelf life of (b) (4) months when stored at 2-8°C. The three process validation lots have been placed on stability. Descriptions of all batches placed on stability are provided in the following table copied from the table.

Lot Tested	Stability Protocol	Manufacturing Process	Manufacturing Site	Stability Container Closure
Commitment lots				
020F15 021F15 004K15	SP-01180	Process 3 Commercial	(b) (4)	1 mL prefilled syringe (b) (4) (b) (4) 30 mg presentation
Primary lots				
026A13/ 026A13A	SP-01125	Process 3 Clinical	(b) (4)	1 mL prefilled syringe (b) (4) (b) (4) 30 mg presentation
002C14/ 002C14A	SP-01125			
001L14/ 001L14A	SP-01175			
004I12A/ 004I12B	DSP-563304			1 mL prefilled syringe (b) (4) (b) (4) (b) (4) mg presentation
005I12A/ 005I12B	DSP-563305			1 mL prefilled syringe (b) (4) (b) (4) (b) (4) mg presentation

The stability studies include the following:

- long term studies at 2-8°C for 36 months (recommended)
- accelerated conditions at 23-27°C/55-65% RH
- stress conditions at 38-42°C/70-80% RH

The stability protocol includes container closure integrity and sterility at the recommended storage temperature (2-8°C). The data, included in section 3.2.P.8 meet specifications for endotoxin and sterility for the duration of the study (36 months).

Reviewer comment: The stability for drug product commitment does not include endotoxin testing but includes sterility testing. The stability protocol should be revised to use container closure integrity testing in lieu of sterility on an annual basis through expiry. Stability studies should also include endotoxin testing done annually and at expiry.

INADEQUATE

CONCLUSION

I. The BLA is recommended for approval from a microbiology product quality perspective.

II. CMC product specific information and data should be reviewed by the OBP reviewer.

III. No additional inspectional follow-up items were identified.

Dupeh Palmer-Ochieng

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First Approval for Indication

Recommendation: Complete Response

BLA 761070
Review

Date: July 12, 2017

From: Sarah Kennett, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Through: Kathleen Clouse, Ph.D.
Director, DBRR I/OBP/OPQ

Drug Name/Dosage Form	**benralizumab/injection (Trade name pending)**
Strength/Potency	**30 mg/1.0 mL prefilled syringe**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype**
Applicant/Sponsor	**AstraZeneca AB**
US agent, if applicable	**AstraZeneca Pharmaceuticals LP**

Product Overview

Benralizumab is a humanized afucosylated IgG1κ monoclonal antibody produced in CHO cells. Benralizumab targets the α chain of the IL-5 receptor (IL-5Rα) and when bound to IL-5Rα on eosinophils (or other IL-5Rα positive cells), 1) blocks the binding of IL-5 to the IL-5 receptor and downstream signaling and 2) activates ADCC, leading to a reduction in eosinophil levels. Benralizumab drug product is supplied at 30 mg/1.0 mL as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in pre-filled syringes (PFS). Benralizumab is proposed as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype.

Product Quality Review BLA 761070 benralizumab

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jennifer Swisher	DBRR I/OBP/OPQ
Drug Product	Jennifer Swisher	DBRR I/OBP/OPQ
Immunogenicity	Jennifer Swisher	DBRR I/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Zhong Li	DIA/OPF/OPQ
Microbiology (DS)	Maria Jose Lopez-Barragan	DMA/OPF/OPQ
Microbiology (DP)	Candace Gomez-Broughton	DMA/OPF/OPQ
Business Process Manager	Kelly Ballard	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Sarah Kennett	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Kathleen Clouse	DBRR I/OBP/OPQ
Microbiology Team Lead	Maria Reyes Candau-Chacon Dupeh Palmer	DMA/OPF/OPQ DMA/OPF/OPQ
Facilities Team Lead	Zhihao Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Colette Jackson	DPARP/ODEII/OND
Cross-disciplinary Team Lead	Lydia Gilbert McClain	DPARP/ODEII/OND
Medical Officer	Sofia Chaudhry	DPARP/ODEII/OND
Pharm/Tox	Timothy Robison	DPARP/ODEII/OND
Clinical Pharmacology	Sury Sista	DPARP/ODEII/OND
Stats	Yu Wang	DBII/OB/OTS

a. Names
   i. Proprietary Name: Pending
   ii. Trade Name: Pending
   iii. Non-Proprietary/USAN: benralizumab
   iv. CAS name: 1044511-01-4
   v. INN Name: benralizumab
   vi. OBP systematic name: MAB HUMANIZED (IGG1) ANTI Q01344 (IL5RA_HUMAN) [MEDI563]

b. Pharmacologic category: Interleukin-5 receptor alpha-directed cytolytic monoclonal antibody

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Acting Branch Chief	Dupeh Palmer	See Panorama
Facilities Branch Chief	Peter Qiu	See Panorama
OBP Review Chief OBP/DBRRI	Sarah Kennett	See Panorama
Director OBP/DBRRI	Kathleen Clouse	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761070/0000	11/16/2016	OBP, DMA, DIA
761070/0011	4/4/2017	OBP, DMA, DIA
761070/0016	5/25/2017	OBP
761070/0019	6/30/2017	OBP
761070/0020	7/10/2017	OBP, DMA

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]
(b) (4)				1	Deficient
				1	Adequate
				3	N/A
				3	N/A
				3	N/A

[1] Action codes for DMF Table: 1 – DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

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

C. Other Documents: None

3. CONSULTS: CDRH re syringe system

Product Quality Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, does not recommend approval of STN 761070 for benralizumab manufactured by AstraZeneca AB. The data submitted in this application are not adequate to support the conclusion that the manufacture of benralizumab is well controlled and leads to a product that is pure and potent. It is recommended that this product not be approved for human use.

b. CR action letter language

1. Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on [To be communicated]. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. Media fill studies for the Drug Product filling line were not included in the submission. Therefore, consistent (b) (4) Drug Product processing was not demonstrated, and continued sterility of the product is not supported. Submit data from media fill studies performed on the filling line and using the specific processing and filling equipment utilized for the manufacture of benralizumab Drug Product.

We also acknowledge receipt of your amendment dated [TBD- response not yet submitted], which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

c. Benefit/Risk Considerations

Benralizumab is proposed as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. Two other antibody products, mepolizumab and reslizumab, have recently been approved for the same indication. While the specific mechanisms by which these antibodies function are not exactly the same, they target the same cell types and general signaling pathways (i.e., eosinophils that express and are impacted by IL-5 receptor). Benralizumab binds to the α subunit of human IL-5R and to FcγRIIIa and mediates ADCC activity. In addition, it blocks the binding of IL-5 to the receptor. IL-5R is expressed on eosinophils and basophils, and IL-5 is a hematopoietic cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils. Eosinophilic inflammation is common in asthma, and eosinophils and basophils are thought to play key roles in the pathogenesis and severity of asthma. Increased levels of eosinophils have been found in the airways of patients with chronic bronchial asthma. Administration of benralizumab, mepolizumab, or reslizumab leads to

depletion of eosinophils, and the currently approved products provide clinical benefit. The risk/benefit analysis of benralizumab product quality was undertaken with consideration that there are commercially available products for the proposed indication.

The overall control strategy for benralizumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The proposed manufacturing control strategy, in-process controls, process monitoring tests, release, and stability testing is currently not sufficient to ensure process consistency and Drug Substance (DS), (b) (4) Drug Product (DP) that have appropriate quality and are free of adventitious agents.

The control of DP manufacturing and safety is supported, in part, by the DP manufacturing facility Drug Master File (DMF). This DMF was determined to be inadequate to support the BLA and a deficiency letter was sent to the DMF holder. The DMF deficiencies must be adequately addressed to demonstrate acceptable DP manufacturing and quality standards. The capability of the DP manufacturing facility to continually process DP (b) (4) has not been demonstrated, because media fill studies were not performed using the equipment utilized for the manufacturing of benralizumab. Data from acceptable studies should be submitted to confirm routine (b) (4) processing and provide assurance of the sterility of the DP released to the market.

There are numerous additional issues with the DS, (b) (4) DP control strategy that have not been resolved during the review cycle. There has been communication with the applicant regarding the majority of the issues, including many requests for additional data or other information to allow for completion of the review. Aspects of the control strategy for which there remain unresolved issues include batch release and stability specifications, expiry periods for the DS and DP, Reference Material (RM) qualification, Working Cell Bank (WCB) qualification and cell bank stability, DS manufacturing process parameters, (b) (4) protocols, and raw material controls. A number of these issues are described in more detail below.

(b) (4)

(b) (4). In addition, the proposed acceptance criteria for numerous critical quality attributes are not supported by clinical batch data or overall manufacturing experience and product understanding. The potency acceptance criteria for (b) (4) DP allow for in vitro activity levels that are significantly lower than the activity levels of the materials used in clinical studies, and no justification for the lower potency levels was provided. In addition, one of the Critical Quality Attributes (CQAs) for benralizumab is (b) (4) (b) (4) can significantly impact potency and may also impact PK through a potential effect on FcRn binding. The applicant proposes to not specifically monitor this attribute, but formation of this variant will impact the charge profile of the antibody, which is

controlled through an isoelectric focusing based assay (cIEF). While significant changes in this attribute will be observed through the potency results, a more direct assessment of the modification may be more sensitive and allow for detection of potential issues in a more meaningful timeframe. However, the proposed acceptance criteria for the relevant cIEF parameter would not allow for control over potential changes in this attribute. Therefore, the applicant was requested to tighten both the potency and cIEF criteria or, in lieu of tightening the cIEF criterion, implement a specific assay for controlling the levels of the relevant deamidated variant. Other CQAs for which the proposed acceptance criteria or test methods were not justified include identity, visible particles, color, clarity, and osmolality; these attributes may directly impact safety and efficacy of the product, impact stability of the material, or indicate that the material is unacceptable. The applicant has been requested to make adjustments to the specifications and provide additional information to support some of the tests performed.

The expiry periods proposed for both the DS and DP were based on data obtained from testing material manufactured using the clinical manufacturing process, rather than the commercial manufacturing process. Given the types of process changes, the comparability data provided, and the stability profiles, it was determined that it is reasonable to use the (b) (4) month real-time clinical DS data to support an expiry period for materials under the recommended frozen storage conditions but that extending the expiry period beyond the available data is not warranted; it was also determined that real-time stability data are needed to fully support the DP expiry period, but the clinical process materials provide sufficient support for setting an initial expiry period that is extended slightly beyond the 18 months for which real-time commercial data are currently available. Therefore, the applicant was requested to limit the DS and DP expiry periods to (b) (4) months and 24 months, respectively.

The qualification protocols for both new RM that is used to evaluate and control potency and other attributes and new production cell line WCB are not acceptable, although both have been updated during the review cycle based on Agency requests. The RM protocol does not include potency acceptance criteria that are sufficient to provide assurance of consistency of potency over the lifecycle of the product, and it is not clear that the criteria for some additional attributes are meaningful with respect to ensuring consistent product quality. The WCB protocol does not include criteria by which the new cell bank will be compared to the current cell bank, e.g., with respect to performance/growth characteristics or resulting product quality. Similarly, the validation protocols (b) (4) are insufficient with respect to the proposed evaluation of impact to CQAs. Therefore, additional updates to the protocols have been requested.

(b) (4)

(b) (4)

[redacted]

We conclude that the current control strategy is deficient with respect to control of the manufacturing of DP and assurance that the DP that would be marketed would remain safe and effective. This assurance can only be provided though a response to the deficiencies communicated regarding the DP manufacturing facility DMF. Additional issues with the benralizumab control strategy that currently does not support the expected level of control over benralizumab potency and other CQAs related to PK and safety may be resolved in response to the most recent information request communicated to the applicant or following additional communications with the applicant. Given the availability of other products for the proposed indication, it is recommended that an approval action not be taken until these deficiencies are resolved.

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

N/A due to recommendation of Complete Response

[redacted]

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II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance, (b) (4), and drug product.

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Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Drug Substance (DS), (b) (4) and Drug Product (DP) CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, deamidation, and fragmentation. Minimal change is expected during storage through expiry.	(b) (4)	No CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Safety/Immunogenicity and potentially PK	Manufacturing process and exposure to heat stress. Minimal change is expected during storage through expiry.		
Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat and potentially extreme light stress.		N/A

		A small increase in fragments is expected during (b) (4) DP storage.	(b) (4)	
Glycosylation (b) (4)	Efficacy (ADCC activity/FcγRIIIa binding)	(b) (4) No change is expected during storage.		(b) (4)
Glycosylation (b) (4)	PK	(b) (4) No change is expected during storage.		
Heavy chain (b) (4)	Efficacy(FcγRIIIa binding) and potentially PK (FcRn binding)	Manufacturing process and exposure to heat stress. Minimal change is expected during storage under recommended conditions.		It is not clear how (b) (4) occurs under some heat stress conditions; therefore, appropriate controls should be implemented.
Heavy Chain (b) (4)	PK (FcRn binding)	Manufacturing process and exposure to heat and light		Requires substantial

(b) (4)		stress. Minimal change is expected under recommended storage conditions.	(b) (4)	stress to generate a clinically meaningful impact.
Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
pH	Safety and Efficacy	Formulation		N/A
Protein Content	Efficacy	Manufacturing process		N/A
Polysorbate 20	Safety and efficacy (control of degradation)	Formulation		N/A

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

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (4) (b) (4)		N/A

			(b) (4)	
Residual (b) (4) (Process-related impurity)	Safety	(b) (4)		
Residual (b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		N/A
Leachables (Process-related	Safety	Process-related impurities potentially from manufacture and		N/A

impurity)		the DS container closure system	(b) (4)	
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through raw materials and throughout the manufacturing process		N/A

a. Description

Benralizumab is a recombinant, humanized afucosylated IgG1κ monoclonal antibody and consists of two heavy chains that are each composed of 451 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 301 (Asn301). The molecular weight of deglycosylated benralizumab without C-terminal lysine is 144,801 Da.

The extinction coefficient was calculated and confirmed experimentally to be 1.43 $(mg/mL)^{-1}$ cm^{-1}. This value has been used during development and will continue to be used to determine the benralizumab protein concentration for commercial use.

b. Mechanism of action

Benralizumab binds to the α subunit of human IL-5R and to FcγRIIIa and mediates ADCC activity. In addition, it blocks the binding of IL-5 to the receptor. IL-5R is expressed on eosinophils and basophils. Interleukin-5 is a hematopoietic cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils. Eosinophilic inflammation is common in asthma, and eosinophils and basophils are thought to play key roles in the pathogenesis and severity of asthma. Increased levels of eosinophils have been found in the airways of patients with chronic bronchial asthma. In vivo, administration of benralizumab leads to depletion of eosinophils. Benralizumab does not elicit CDC activity.

c. Potency Assay

A cell-based bioassay that measures activation of cell signaling as a surrogate measurement of ADCC activity is used to control drug substance (DS), (b) (4) and drug product (DP) potency. A natural killer cell line (NK-92) engineered to express FcγRIIIa and a luciferase reporter gene under control of an NFAT element is used as the effector cells, and a CTLL-2 cell line that expresses IL-5Rα on the surface is used as the target cells. The addition of benralizumab leads to bridging of the target and effector cells, clustering of FcγRIIIa, and the induction of signaling. The amount of luciferase generated is measured using a chemiluminescent substrate and is proportional to ADCC activity. Dose-response curves are analyzed, and the potency of test articles is calculated as a percentage relative to the reference material (RM).

d. Reference material(s)

(b) (4)

e. Critical starting materials or intermediates

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4) The container closure system is suitable for benralizumab, based on stability data and maintenance of closure integrity.

h. Dating period and storage conditions

The dating period for the DS will be (b) (4) months when stored at (b) (4) °C.

C. (b) (4) Drug Product [benralizumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product (b) (4) CQAs that are derived from the (b) (4) drug product manufacturing process (b) (4) and drug product attributes.

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (DP [redacted] (contaminant)	Safety (infection) and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination introduced throughout [redacted] DP manufacturing process or due to failure of container closure integrity	[redacted]	[redacted] processing qualification is currently a CR issue (see CR letter language above).
Container Closure Integrity (contaminant)	Safety (contamination)	Manufacturing failure or impact of storage conditions		N/A
Endotoxin (contaminant)	Safety and Purity	Contamination introduced throughout [redacted] DP manufacturing process or due to failure of container closure integrity		N/A
Color and turbidity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Particulate Matter (translucent, visible and subvisible)	Safety/ Immunogenicity	Manufacturing process and CCS		N/A

(Product or Process Related Impurities)			(b) (4)	
Polysorbate 20 concentration	Safety and Efficacy (control over degradation)	Manufacturing process		N/A
Deliverable Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Breakloose and Glide Force (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		Additional justification requested; if additional data are required, they will be addressed as a PMC.

a. Potency and Strength

Benralizumab is supplied at 30 mg/1.0 mL syringe. Potency is defined as the percent activity relative to the current benralizumab RM. The potency assay is the same as described in the DS section of this memo.

b. Summary of Product Design

Benralizumab is supplied as a sterile, single-dose, preservative-free solution for SC injection in a pre-filled syringe. Benralizumab DP is formulated in 9 mM histidine, 11 mM histidine hydrochloride monohydrate, 250 mM α,α-trehalose dehydrate, and 0.006% (w/v) polysorbate 20, pH 6.0. The extractable volume is 1.0 mL.

c. List of Excipients

Excipients include 9 mM histidine, 11 mM histidine hydrochloride monohydrate, 250 mM α,α-trehalose dehydrate, and 0.006% (w/v) polysorbate 20. All excipients are compendial; the histidine hydrochloride monohydrate follows the requirements of Ph.Eur. and JP, because there is no USP monograph/chapter for this material.

d. Reference material(s)

The same reference material is used for DS and DP.

e. Manufacturing process summary

(b) (4)

f. Container closure

(b) (4)

The primary container closure system for benralizumab DP (b) (4)

Combined with the current stability and clinical data, the compatibility studies performed for the container closure systems are adequate to support a sufficiently low risk to allow initial marketing; however, the responses to the most recent IR will dictate whether a PMC related to container closure leachables will be requested.

The secondary container closure system consists of a tray insert that is placed into a paperboard carton.

g. Dating period and storage conditions
The dating period for benralizumab DP will be 24 months when stored at 2-8°C, protected from light.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Store in original carton (b) (4)
- Protect from light (b) (4)
- Do not freeze.
- Do not shake.

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F. Establishment Information

OVERALL RECOMMENDATION: pending as of 7/12/17				
DRUG SUBSTANCE				
Site Name	**Address**	**FEI/DUNS Number**	**Responsibility**	**Final Recommendation**
AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC)	633 Research Court Frederick, MD 21703 USA	FEI# 3002617771	Preparation of Future Working Cell Banks; Storage and maintenance of Master and Working Cell Banks; Drug Substance manufacture and Storage; Drug Substance release and stability testing	Pending OPF/DIA review of the 5/15-23/2017 PAI
MedImmune LLC	1 MedImmune Way Gaithersburg, MD 20878 USA	DUNS # 489176682	Preparation of Working Cell Bank Lot 08BG03	No further evaluation necessary per ICH Q7
(b) (4)				No further evaluation necessary per ICH Q7
DRUG PRODUCT				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
(b) (4)			Drug Product manufacture; Release testing for sterility and Endotoxin; Stability testing for sterility; Labeling and packaging	Acceptable based on PAI of (b) (4)
MedImmune UK Ltd.	MedImmune UK Ltd. 6 Renaissance Way Liverpool, L24 9JW United Kingdom	FEI# 3004066112	Release testing	Acceptable based on PAI of 2/13-17/2017
AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC)	633 Research Court Frederick, MD 21703 USA	FEI# 3002617771	Release testing	Pending OPF/DIA review of the 5/15-23/2017 PAI

G. Facilities

The BLA proposes commercial manufacture of benralizumab DS and DP at AstraZeneca Pharmaceutical LP, Frederick, MD, USA (FEI 3002617771) (b) (4) DP release testing will also occur at MedImmune UK Ltd., Liverpool, UK (FEI 3004066112).

A Pre-license Inspection was performed at AstraZeneca Pharmaceutical LP, 5/15-23/2017. A three item Form FDA 483 was issued. The initial field recommendation for the firm is VAI and approval of BLA 761070/0; however, the inspection is pending final classification.

A Pre-license Inspection was performed at MedImmune UK Ltd., 2/13-17/2017. The inspection was classified as NAI. The compliance status of this benralizumab DP testing facility is acceptable.

A Pre-license Inspection was also performed at (b) (4) A four-item FDA Form 483 was issued for: 1) inadequate process simulations (b) (4) 2) inadequate QC sample controls; 3) inadequate investigation of particles (b) (4) and 4) inadequate computerized system validation. Withhold approval of BLA 761070 was recommended by the inspection team. An OPF/DIA review of the PLI deemed the firm's response to FDA Form 483 adequate and recommended approval of the individual facility for (b) (4) in regard to BLA 761070 under the SVS profile. The inspection was finalized as VAI. The compliance status of this benralizumab DP manufacturing facility is acceptable.

H. Lifecycle Knowledge Management

a. Drug Substance
   i. Protocols that are approvable: At-scale validation (b) (4)
   ii. Outstanding review issues/residual risk: See CR action language and risk evaluation above
   iii. Future inspection points to consider:
      1. Implementation of appropriate harvest operation discharge interval
      2. Review of updated potency assay SOPs to ensure independent assay control is required and of trending of RS and assay control EC50 results
      3. Review of system suitability requirements for the cIEF assay

b. Drug Product
   i. Protocols that are approvable: None
   ii. Outstanding review issues/residual risk: See CR action language and risk evaluation above
   iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	x		
2.	Naturally Derived Product		x	
3.	Botanical		x	
4.	Human Cell Substrate/Source Material		x	
5.	Non-Human Primate Cell Substrate/Source Material		x	
6.	Non- Primate Mammalian Cell Substrate/Source Material	x		
7.	Non-Mammalian Cell Substrate/Source Material		x	
8.	Transgenic Animal Sourced		x	
9.	Transgenic Plant Sourced		x	
10.	New Molecular Entity	x		
11.	PEPFAR Drug		x	
12.	PET Drug		x	
13.	Sterile Drug Product	x		
14.	Other_____		x	
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence		x	

	Linked to the Application (#_____)				
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	
Quality Considerations					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements		x		
27.	Real Time Release Testing (RTRT)			x	
28.	Parametric Release in lieu of Sterility Testing			x	
29.	Alternative Microbiological Test Methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial Analytical Procedures	Drug Product	x		
32.		Excipients		x	

33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other _____			x	

APPEARS THIS WAY ON ORIGINAL

Dupeh Palmer-Ochieng

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Date: 7/14/2017 01:54:09PM
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Kathleen Clouse Strebel

Digitally signed by Kathleen Clouse Strebel
Date: 7/14/2017 02:01:20PM
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Sarah Kennett

Digitally signed by Sarah Kennett
Date: 7/14/2017 01:53:44PM
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Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 7/21/2017 09:46:59AM
GUID: 508da7480002bfb5825e149b2b4eb91d

U.S. FOOD & DRUG ADMINISTRATION

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

Date: 7/13/2017

To: Administrative File, STN 761070/0

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

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

Subject: New Biologic License Application (BLA)

US License: 2043

Applicant: AstraZeneca AB

Facilities: MedImmune LLC Frederick Manufacturing Center (FMC)
633 Research Court, Frederick, 21703 Maryland
FEI: 3002617771 (DS manufacture)

Product: Benralizumab (trade name pending); internal company codes: MEDI-563, 01P003

Dosage: Sterile solution for subcutaneous injection (30 mg/mL)

Indication: Add-on maintenance treatment for severe asthma with eosinophilic phenotype in adults

Goal date: 11/13/2017

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

Review Summary

AstraZeneca AB has submitted BLA 761070 to obtain approval of benralizumab, a humanized, afucosylated, monoclonal antibody of the IgG1/κ-class selective for interleukin-5Rα indicated for the add-on maintenance treatment of adults with severe asthma with eosinophilic phenotype.

BLA 761070 was submitted in eCTD format on 11/16/2016. This review memo evaluates information on benralizumab drug substance section of the BLA from a product quality microbiology perspective. The review of benralizumab drug product section of the BLA was performed by Candace Gomez-Broughton.

Drug Substance Microbiology Quality Information Reviewed

IR Submission Date	Description	eCTD Sequence	Date
Not applicable	Original BLA	0000	11/16/2016
6/21/2017	Response to information request	0020	7/10/2017

3.2.S DRUG SUBSTANCE

S.1 GENERAL INFORMATION

Benralizumab is a recombinant humanized afucosylated IgG1κ monoclonal antibody directed against the human interleukin (IL)-5 receptor alpha subunit expressed on eosinophils and basophils. Benralizumab is comprised of two heavy chains and two light chains with an overall molecular weight of approximately 150 kDa. Benralizumab depletes eosinophils via a mechanism of antibody-dependent cellular cytotoxicity (ADCC).

The description is satisfactory

S.2 MANUFACTURE

S.2.1 MANUFACTURE(S)

Table S.2.1.-1 below (reproduced from the submission) summarizes the facilities involved in the manufacture (b) (4) and release testing for benralizumab drug substance:

Table S.2.1-1 Drug Substance Manufacturing and Testing Sites

Name and Address	Facility Identifier	Responsibilities
(b) (4)		
MedImmune LLC 1 MedImmune Way Gaithersburg, MD 20878 USA	DUNS 489176682	• Preparation of Working Cell Bank Lot 08BG03
MedImmune LLC Frederick Manufacturing Center (FMC) 633 Research Court Frederick, Maryland 21703 USA	FEI: 3002617771 DUNS 968459953	• Preparation of Future Working Cell Banks • Storage and maintenance of Master and Working Cell Banks • Drug Substance manufacture and storage • Drug Substance release and stability testing

DUNS = Data Universal Numbering System Number; FEI = Facility Establishment Idenitifier

Reviewer's comment: a pre-license inspection (PLI) was conducted at the benralizumab drug substance manufacturing facility (Frederick Manufacturing Center, FMC) from May 15th through May 23rd 2017 (see under MARCS Operation ID No. 58885).

Satisfactory

S.2.2 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

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(b) (4)

[redacted]

CONCLUSION

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

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

III. A pre-license inspection was conducted at MedImmune LLC Frederick Manufacturing Center (FMC), from May 15th through May 23rd, 2017 by OGROP/ORA/OMPTO/OBPO/BPIS (Arie Menachem) and CDER/OPQ/OBP/DBRRIV (Jennifer Swisher); see under MARCS Operation ID No. 58885.

FDA Information Request for STN 761070/0 submitted on 06/21/2017. Sponsor responses in amendment 0020 dated 7/10/2017

Section 3.2.S.2.2, Description of Manufacturing Process and Process Controls

(b) (4)

Section 3.2.S.2.4, Control of Critical Steps and Intermediates

7. Provide bioburden and endotoxin action limits in section 3.2.S.2.4 of the BLA.

Section 3.2.S.2.5, Process Validation

(b) (4)

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 761070	**Submission Type: BLA**	**Established/Proper Name: benralizumab**
Applicant: AstraZeneca AB	**Letter Date: 11/16/2016**	**Dosage Form: Injection, solution**
Chemical Type: humanized, afucosylated, monoclonal antibody, immunoglobulin G1 kappa (IgG1k)	**Stamp Date: 11/16/2016**	**Strength: 30 mg** (b) (4)

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	None to be included in 74 day letter; more will be sent as needed throughout the review cycle.

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

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B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☒	☐	
19.	Other_____	☐	☒	

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Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☒	☐	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☒	☐	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☒	

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

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices	☒	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using	☒	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*)	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☒	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	

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C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
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?	☐	☒	☐	Nothing in a foreign language
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients	☒	☐	☐	– There is no facility and equipment information provided in Module 3, Section 3.2.A. – Facility and equipment information for (b) (4) in Module 3, Section 3.2.P.3.1. – Facility and equipment information for MedImmune LLC, FMC, Frederick, Maryland is referred to DMF (b) (4) in Module 3, Section 3.2.S.2.1. – Letters of Authorization are provided in Module 1, Section 1.4.2.
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☒			Drug product validation reports for rabbit pyrogen test and for LAL USP <85> were provided in 3.2.R and in P.5.3, respectively.

Jennifer Swisher

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