CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761058Orig1s000

CHEMISTRY REVIEW(S)

Office of Pharmaceutical Quality Integrated Review
BLA 761058 Cyltezo (Adalimumab-adbm)
August 25, 2017

Application Team Lead: Howard Anderson, PhD, Lead Biologist OBP/DBRRIII
Tertiary Reviewer: Susan Kirshner, PhD, Review Chief OBP/DBRRIII (Maria Gutierrez Lugo proxy for Susan Kirshner)

OPQ Recommendation: OPQ recommends approval of this BLA for production of Cyltezo filled in pre-filled syringes, with two product quality post-marketing commitments (PMC) and one microbial PMC. This Integrated review updates and replaces the July 28, 2017, Integrated review in panorama.

Justification

The results reviewed by OBP support a determination that Cyltezo is highly similar to US-licensed Humira. The manufacture of Cyltezo drug substance (DS) and drug product (DP) is validated and well controlled and produces a product that is pure and potent. The sponsor has agreed to a post marketing commitments to develop a comprehensive and robust control strategy to control for effector function of BI 695501 located in section 1.C. of this review. The DS manufacturing process is robust for inactivation or removal of viral adventitious agents. The manufacturing process is demonstrated to be consistent by the production of nineteen DS and thirty one DP lots. Clinical study lots were evaluated in the analytical similarity study. The manufacturing process for the clinical material, process validation material, and the commercial process material are identical. The (b) (4) DP two year expiry is supported with real time stability results from multiple lots.

The immunogenicity assays used to evaluate antidrug antibodies (ADA) are adequately validated. Patients developed similar binding and neutralizing responses to Cyltezo and US-licensed Humira.

The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. Significant deficiencies associated with the DP manufacturing at (b) (4), identified during this review have been resolved by the removal of (b) (4) as a DP manufacturing facility in a July 24, 2017, amendment to the BLA. The applicant committed to conducting one microbial PMCs located in section 1.C of the review.

The DIA reviewer is recommending approval of the commercial manufacture of BI Cyltezo DS and DP at the Boehringer Ingelheim Fremont Inc. (BIFI) facility in Fremont, California (FEI 3005925062). Assembly and secondary packaging of the PFS occurs at BIFI. (b) (4) is used as a testing site of the DS and DP. The OBP product quality and analytical, immunogenicity assay, DMA DS and DP microbiological, and DIA facility technical reviews are located as separate documents in Panorama.

BLA 761058 Cyltezo (Adalimumab-adbm) QUALITY REVIEW

Drug Name/Dosage Form	Cyltezo (BI 695501)/Solution in Pre-Filled syringe
Strength/Potency	40 mg/0.8 ml
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis, and Plaque Psoriasis
Applicant/Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
US agent, if applicable	NA

Product Overview

Cyltezo is an IgG1 subclass humanized proposed biosimilar to the US-licensed Humira monoclonal antibody and is produced (b) (4) using recombinant DNA technology. Cyltezo blocks the inflammatory action of Tumor Necrosis Factor alpha (TNFα) by binding soluble and transmembrane TNFα and prevents the cytokine from binding to p55 (TNFR1) and p75 (TNFR2) cell surface receptors. TNF is produced primarily by macrophages in response to inflammatory stimulus such as lipopolysaccharide. TNF can also be produced by NK cells, neutrophils, mast cells, eosinophils, and neurons. TNFR1 (CD120a) is expressed on most cells while TNFR2 (CD120b) is expressed on cells of the immune system. TNF binding to receptors activates the NF-kB pathway stimulating cell proliferation and survival, as well as stimulating immune responses. TNF receptor binding can also trigger apoptotic cell death. Cyltezo contains a single Fc N-glycosylation site at Asn301 on both heavy chains that contributes to Fc-mediated effector functions.

Cyltezo is being developed for all US-Licensed Humira non-exclusive indications that include, Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (4 years of age and older), Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, and Plaque Psoriasis. Two clinical studies are being used to support approval of this BLA. The first clinical trial (1297.8) was a single dose randomized double blind study in healthy individuals to assess PK, immunogenicity, and safety. The second clinical trial (1297.2) was a multi-dose randomized double blind efficacy, safety and immunogenicity study in rheumatoid arthritis patients.

Quality Review Team and Signature Approval Section

OBP Product Quality, DMA Microbiological, DIA Facility, and Immunogenicity Assay technical reviews are archived in Panorama and contain primary and secondary review sign off. Provided below are OPQ staff involved in the review of this BLA. Electronic signatures for Dr. Howard Anderson, the ATL, and Dr. Susan Kirshner, the tertiary reviewer are located at the end of this document.

DISCIPLINE	REVIEWER	OFFICE/DIVISION
Business Regulatory Process Manager	Keith Olin	OPRO
OBP Label Review	Vicky Borders-Hemphill	OBP
DS and DP Product Quality and Analytical Similarity	Richard Ledwidge	OBP/DBRR III
Immunogenicity Assays	Davinna Ligons	OBP/DBRR III

Facilities	Ephren Hunde	OPF/DIA/IABI
Microbiology DS and DP	Monica Commerford	OPF/DMA/MABIV
Application Team Lead	Howard Anderson	OBP/DBRRIII
Facilities Team Lead	Zhihao Peter Qiu	OPF/DIA/IABI
Microbiology Team Lead	Maria Reyes Candau-Chacon	OPF/DMA/BIV
Tertiary OBP Reviewer	Susan Kirshner	OBP/DBRR III

Multidisciplinary 761058 Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Sadaf Nabavian	ODEII/DPARP
Cross-disciplinary Team Lead	Nikaloy Nikolov	ODEII/DPARP
Medical Officer	Stefanie Freeman/Sarah Yim	ODEII/DPARP
Pharm/Tox	Lawrence Leshin/Carol Galvis	ODEII/DPARP
Clinical Pharmacology	Shalini Wickramaratne/ SenarathYapa/Anshu Marathe	OCP/DCPII
Statistics	James Travis/Gregory Levin	OTS/OB/DBII
CMC Statistics	Li Xing/Meiyu Shen/Yi Tsong	OTS/OB/DB/VI

Quality Review Data Summary

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS

A. BLA 761058 OPQ Amendments Reviewed

Submissions Reviewed and Reviewed	Amendment Submission Date
OBP	
Sequence 007 (8)	1/27/2017
Sequence 015 (16)	3/17/2017
Sequence 017 (18)	4/14/2017
Sequence 027 (26)	6/19/2017
DMA DP	
Sequence 002	12/14/2016
Sequence 028	6/26/2017
Sequence 030	6/29/2017
Sequence 022	6/21/2017
Sequence 031	7/5/2017
Sequence 030	7/19/2017
Sequence 032	7/24/2017
DMA DS	
Sequence 023	5/31/2017
Sequence 026	6/30/2017
Sequence 031	7/5/2017

B. DMFs:

DMF Number	Holder	Item referenced	Letter of cross-reference	Comments
(b) (4)			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Referenced in DMA DP Review
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Referenced in DMA DP Review
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Not Reviewed/Adequate Information provided in the BLA
			Yes	Not Reviewed/Adequate Information provided in the BLA

3. NOMENCLATURE

A. Names

i. Proprietary Name: Cyltezo

ii. Trade Name: Cyltezo

iii. Non-Proprietary/USAN: Adalimumab-adbm

iv. INN Name: Adalimumab-adbm

v. Company Code: BI 695501

vi. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [BI 695501]

B. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

4. CONSULTS: There was a consult from the OND RPM to CDRH ODE and OC for the pre-filled syringe (b) (4)

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality recommends approval of Cyltezo manufactured by Boehringer Ingelheim in Fremont, CA. The analytical similarity assessment studies support a determination that Cyltezo is highly similar to US-licensed Humira. Comparative analytical (and other) data submitted by BI provided a scientifically adequate justification to permit the use of comparative data using EU approved Humira, thus providing a scientific bridge to support the toxicology studies conducted with EU approved Humira in this BLA. As summarized in the Justification section of the review OBP, DMA, and DIA reviewers all have concluded that this BLA should be approved.

B. Phase 4 Post-Marketing Commitment Recommendations (draft language)

OBP

1. Develop a comprehensive and robust control strategy to control for effector function of BI 695501.

DMA

1. Conduct the bioburden in-process and release method qualification using two additional batches of BI 695501.

C. Approval action letter language

- Manufacturing location
  - Drug substance – Boehringer Ingelheim Fremont (BIFI), Inc, CA (FEI#3005925062)
  - Drug product – Boehringer Ingelheim Fremont (BIFI), Inc, CA (FEI#3005925062)

- Fill size and dosage form – 40 mg/0.8 ml liquid in pre-filled syringe

- Dating period
  - Drug product – Request for 24 months at 5°C ± 3°C is granted based on three years of real-time results and supporting stability results.

  - Drug substance – Request for (b) (4) months at (b) (4) °C is granted based on 3 years of real-time results and supporting stability results.

- A request for a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (c) is provided in BLA 761058 section 1.12.15. The request has been granted since this molecule is a protein that breaks down naturally in the

environment and the estimated concentration of the product at the point of entry into the aquatic environment will be below 1 part per billion.

- Cyltezo is exempt from lot release and the sponsor is not currently required to submit samples of future lots of Cyltezo to the Center for Drug Evaluation and Research (CDER) for release by the Director, under 21 CFR 610.2.

II. Analytical Similarity

Analytical similarity was demonstrated using 13 Cyltezo lots, 58 US-licensed Humira lots and 86 EU-approved Humira lots. The 13 Cyltezo DP lots analyzed in the analytical similarity studies were produced from 13 DS lots. Two clinical studies are being used to support approval of this BLA. The first was a single dose randomized double blind study in healthy individuals to assess PK, immunogenicity, and safety. The second was a multidose randomized, double blind efficacy, safety, and immunogenicity study in rheumatoid arthritis patients. Cyltezo and US licensed-Humira were evaluated in two clinical studies and the analytical similarity study and will be used for the commercial material. The Cyltezo material that was evaluated in the analytical similarity studies was also evaluated in the clinical studies. There have been no major process changes during development.

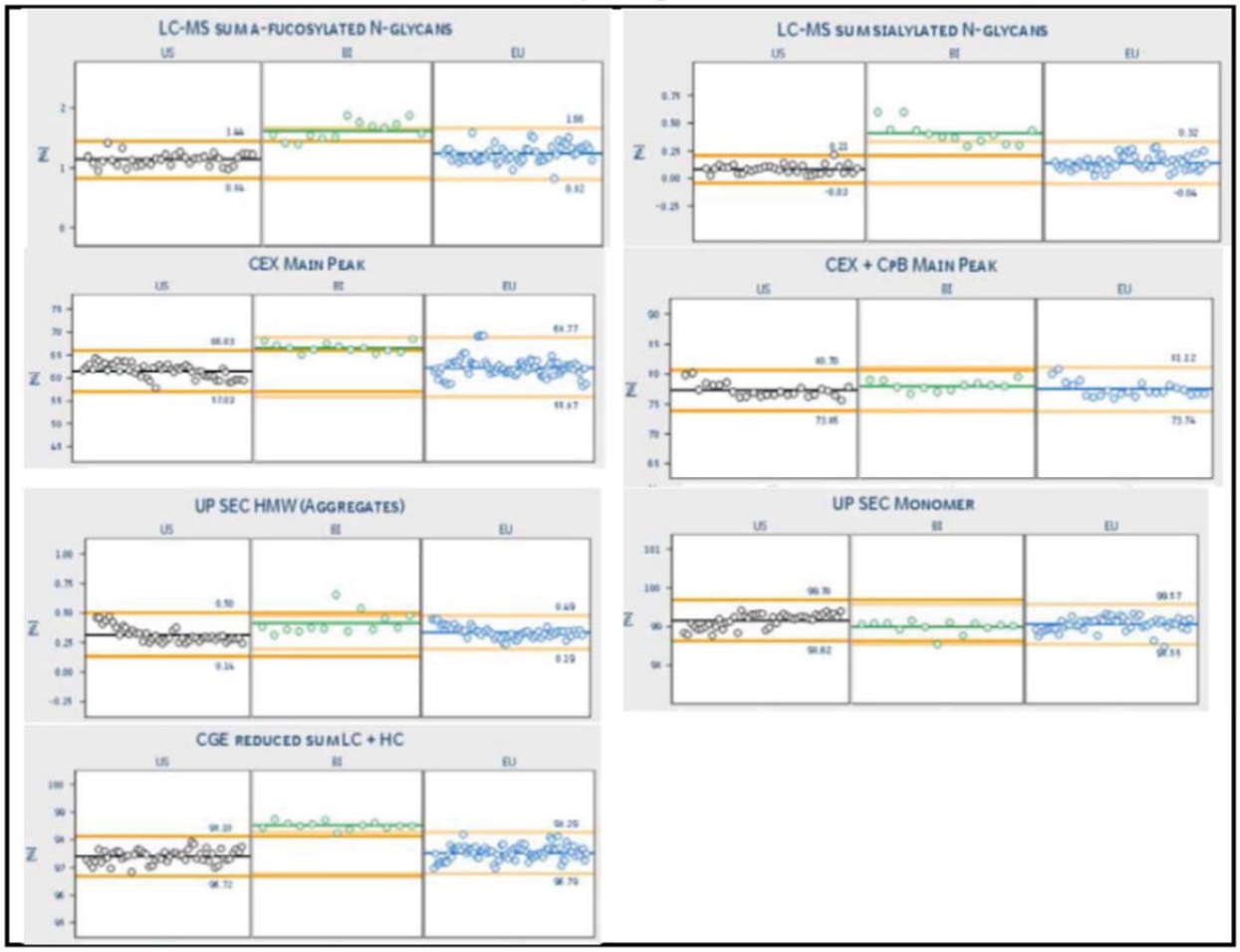
Provided below is a modification of the sponsor's Table 1 that summarizes the analytical similarity study results provided in Report q002352228-02. In summary, all parameters assessed in the Tier 1 statistical equivalence range, and 90% of the BI lots assessed in the Tier 2 US-Licensed Humira quality statistical range met the predefined acceptance criteria. Minor differences were noted in the Tier 2 statistical attributes for N-linked oligosaccharides, (a-fucosylation, a glycosylation, and sialyation), charge variants (CEX assay), size variants (CGE) and aggregates. The differences in all cases were just outside the three standard deviation range (see table 2 below). The difference in these attributes was also observed for the same attributes when analyzed by orthogonal methods in the Tier 3 graphical display analysis. The residual uncertainty raised by these results is mitigated by the results of the functional potency assays (CDC, ADCC and ADCP), showing no meaningful differences between Cyltezo and US-licensed Humira. There were clinically meaningful differences in clinical studies regarding safety, efficacy, immunogenicity, pharmacokinetics and pharmacodynamics.

Table 1		
Tier 1-Equivalence Testing		
Assay	**Assay Parameter**	**Demonstration of similarity**
sTNFa neutralization assay	Inhibition of TNFα induced apoptosis	Yes
TNFa binding assay SPR (RLCA)	Binding activity	Yes
Tier 2 Statistical Quality Range (3 standard Deviations)		
Assay	**Assay Parameter**	**Demonstration of similarity**

		(amount of batches within US licensed Humira Quality Range
TNFa binding SPR (affinity)	Binding affinity	Yes (13/13)
mTNFa competitive binding assay	Binding affinity	Yes (13/13)
ADCC assay	ADCC activity	Yes (13/13)
Reverse signaling assay	Reverse signaling assay	Yes (6/6)
CDC Assay	CDC activity	Yes (13/13)
MLR	Regulatory Macrophage	Yes (5/5)
CD16a (FcRn) Binding SPR (cRLCA)	Fc binding activity	Yes (13/13)
FcRn binding SPR (affinity)	Fc binding activity	Yes (13/13)
N-Carbohydrate structure analysis by LC-MS peptide mapping	Sum of A-Fucosylated and high mannose-N glycans	Yes (13/13)
	High mannose	Yes (13/13)
	A-fucosylated	**Minor Differences (2/13)**
	Hybrid	Yes (13/13)
	Bisecting	Yes (12/13)
	Galactosylated	Yes (12/13)
N-Carbohydrate structure analysis by LC-MS peptide mapping	**Sialyated**	**Minor Differences (0/13)**
	Fucosylated	Yes (13/13)
CEX	Acidic peak group	Yes (12/13)
	Main peak	**Minor quantitative differences (4/13)**
CEX-CpB	Main peak	Yes (12/12)
	Acidic peak group	Yes (12/12)
UP SEC	**Aggregates**	**Minor quantitative differences (11/13)**
	Monomer	Yes (12/13)
	Fragments	Yes (13/13)
CGE reduced	HC	Yes (12/13)
	LC	Yes (13/13)
	Pre HC	**Minor quantitative differences (0/13)**
	Sum of LC+HC	**Minor quantitative differences (0/13)**
	LWM	Yes (13/13)
CGE non reduced	LMW	Yes (13/13)
	Monomer	Yes (13/13)
LC-MS peptide mapping	Methionine oxidation within CDR / Fc receptor binding site	Yes (13/13)
UV scan	Protein Content	Yes (12/13)

Tier 3 Visual Assessment of graphical displays			
Edman sequencing	LC-MS peptide mapping with NEM labeling	LC-MS peptide mapping	Isoaspartate assay
Intact and reduced mass analysis	C1q binding (ELISA)	Oligosaccharide characterization by Oligomap	LC-MS peptide mapping
LC-MS/MS peptide mapping	ADCP assay (CD32 reporter gene assay)	Monosaccharide Analysis	LC-MS reduced mass analysis
CD-far UV	CD16a binding SPR (affinity)	Oligosaccharide characterization by Oligomap	LC-MS peptide mapping
CD-near UV	CD16b binding SPR (affinity)	Monosaccharide Analysis	CGE non-reduced
FT-IR	CD32a binding SPR (affinity)	Oligosaccharide characterization by Oligomap	CGE reduced
DSC	CD32b/c binding SPR (affinity)	Monosaccharide Analysis	AF4
Intrinsic fluorescence	CD64 binding SPR (affinity)	LC-MS peptide mapping	AUC
LC-MS non-reduced peptide mapping		CEX	UP SEC MALS
		CEX+CpB	HIC
		CZE	HIC after CpB treatment

Table 2 Tier 2 Attributes Outside of the Quality Range



III. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below provides a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. Additional information is located in primary DS and DP Product Quality, DS and DP Microbiology Control, and Facility technical reviews in Panorama.

Table 1: DS and DP CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy (b) (4)	Comment
Potency-	Efficacy	Antibody structure is impacted by bioreactor conditions		Stability indicating
Potency-ADCC	Efficacy	Antibody structure is impacted by bioreactor conditions		PMC
Potency-CDC		Antibody structure is impacted by bioreactor conditions		PMC
Charge Variants	Immunogenicity	Can result from slight from variations in manufacturing conditions, heat exposure can increase attribute		Stability indicating
High Molecular Weight (HMW) Impurities	Immunogenicity, Loss of efficacy due to decrease in potency	Heat exposure can increase attribute		Stability indicating
Low Molecular Weight (LMW) Impurities	Loss of efficacy due to decrease in potency	Incomplete antibody assembly during production, heat exposure can increase attribute		Stability indicating
Antibody Fragment, LMW and HMW Impurities	Loss of efficacy due to decrease in potency	Incomplete antibody assembly during production, heat exposure can increase attribute		Stability Indicating
Oxidation and Deamidation	Increase in Immunogenicity	Increase in ADA can reduce potency and PK/PD		Not stability indicating

B. Adalimumab Drug Substance Quality Summary

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to drug substance. For additional information see primary Product Quality and DS Microbiology Controls technical reviews in Panorama.

Table 2. CQA Identification, Rick and Live Knowledge Management

CQA	Risk	Origin	Control Strategy	Comment
Glycosylation	Decrease in fucose has theoretical rick for increase in potencies associated with the Fc region of Cyltezo (ADCC, CDCC/ADCP)	Loss of fucose and increase in high mannose oligosaccharides during production.	(b) (4)	Not stability indicating
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing		PMC for method qualification studies
Endotoxin	Safety and purity	Raw materials or contamination during manufacturing		None
Host cell protein	Safety and immunogenicity	Process-related impurity from the production cells		None
Host cell DNA	Safety	Process-related impurity from the production cells		None
Virus Contamination	Safety	Contamination during manufacturing		None
(b) (4)	Safety and Immunogenicity	(b) (4)		None

Protein Content	Efficacy	Protein is (b) (4) (b) (4)	(b) (4)	None
Appearance, Physical Form Clarity, Color	Safety and Efficacy	Manufacturing process and formulation		None
Identity	Safety and Efficacy	NA		None
Leachable Impurities	Safety	Process-related impurities, and drug substance container closure system		None

1. Description

Critical quality attributes include Cyltezo Fab region binding and neutralizing soluble and cell surface TNFα. Neutralization of soluble TNFα blocks receptor binding. Cyltezo binding to cell surface TNFα can induce reverse cell signaling as well as active regulatory macrophages expressing TNFα. Cyltezo Fc region binding to CD16a receptors mediate antibody induced cell mediated cytotoxicity (ADCC) via NK cells, Fc receptor antibody mediated macrophage dependent phagocytosis, and complement dependent cytotoxicity (CDC). The single N-linked oligosaccharide can control Fc effector functions due to the presence of a glycosylated species, galactosylated species, high mannose species and fucosylated species. Alpha Gal structures and NGAG sialylated species are not present in Cyltezo. Stress studies reveal that deamidation does not occur within the CDR or Fc receptor binding regions.

2. Mechanism of Action (MOA)

Cyltezo blocks the inflammatory action of TNFα by binding soluble and transmembrane TNFα, preventing the cytokine from binding to p55 and p75 cell surface receptors. TNF is produced primarily by macrophages in response to inflammatory stimulus such as lipopolysaccharide. TNF can also be produced by NK cells, neutrophils, mast cells, eosinophils and neurons. TNFR1 (CD120a) is expressed on most cells while TNFR2 (CD120b) is expressed on cells of the immune system. TNF binding to receptors activates the NF-kB pathway stimulating cell proliferation and survival, as well as stimulating the immune response. TNF can also stimulate cell death by apoptosis. Cyltezo contains a single Fc N-glycosylation site at Asn301 on both heavy chains that contributes to Fc-mediated effector functions. Cyltezo mechanism, as described in 1 above includes CDC and ADCC Fc-mediated effector functions through CD16, CD32, CD64 binding, reverse signaling through membrane bound TNFα, and activation of regulatory macrophages. Thus inhibition of multiple TNF α immunological pathways contributes to Cyltezo MOA.

3. Potency

Two potency methods are used for DS and DP release and stability testing. For the cell based method Potency is defined relative to a qualified reference standard. The cell based potency method quantifies the inhibition of TNFα induced apoptosis of a U-937 cell line by binding and neutralizing soluble TNFα. Viable cells are quantified by flow cytometry. Potency is calculated

relative to reference material using dose response curves for a four-parameter logistic statistical model. Half maximal inhibitory concentration is calculated as the EC50 value. The method is appropriately validated and has the appropriate method suitability controls, including a control for parallel dose responses cures (coefficient of determination) for samples and the reference material (RS). The cell based assay specification is (b) (4) % of RS. The release and stability testing program also includes a TNFα binding assay that uses a Biocore response level correlation assay. In the method protein A/G is immobilized to bind mobile phase 1 injected test and control samples and mobile phase 2 soluble TNFα. Dissociation constants are determined by measuring the dissociation of TNFα and Cyltezo. The binding assay acceptance criterion is (b) (4) of RS. Additional potency assay information is located in the product quality technical review.

4. Reference Standard (RS)

The sponsor has established a two tiered RS qualification program as per ICH Q6B recommendations. Both primary PS01 RS is stored at (b) (4) and derived from clinical material. The primary PS01 RS is used to anchor future working reference standard attributes (e.g. potency, purity, etc.) to the Cyltezo product quality attributes evaluated in the clinical studies. The working RS is stored at (b) (4) and is used for routine analytical testing. The Cyltezo primary RS PS01 and working RS WS01are derived from DS lot 6013165 and is representative of the (b) (4) L commercial process. This lot was used to produce DP lot 403841 that was evaluated in clinical study 1297.2 and the analytical similarity study. Additional information is located in the product quality review. A protocol is provided for the qualification of future primary and working RS and the protocol contains an adequate release and characterization testing strategy with acceptance criteria.

5. Manufacturing Process Summary

(b) (4)

6. Container closure

The DS container closure is a (b) (4) The (b) (4) were qualified with regard to storage

(b) (4), gas permeation and solvent loss, transport validation, container integrity testing, Biocompatiblity meets USP and Ph.Eur CC requirements, and acceptable leachable and extractable studies support the suitability of the CC.

7. Dating period and storage conditions

Thirty-six months of real time stability results for 2 DS lots and 24 months real time stability data for 4 DS lots are provided to support the proposed (b) (4) month DS expiry when stored at -(b) (4)°C. A commitment is made that one lot of DS will be place on long term stable for 4 years at the normal storage condition, at (b) (4) for °C accelerated conditions, and 1 year at (b) (4)°C stress conditions. The testing program strategy and testing frequency are adequate and consistent with ICH Q5C recommendations.

C. Cyltezo Drug Product Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information see primary Product Quality and DP Microbiology Controls technical reviews in Panorama.

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

CQA	Risk	Origin	Control Strategy	Comment
Sterility (contaminant)	Safety (Infection), Purity and Efficacy via degradation or modification of products by contaminating microorganisms	Contaminants could be introduced during the manufacturing process or by failure of container integrity	(b) (4)	None
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Contaminants could be introduced throughout DP manufacturing or due to integrity failure		None
Particulate Matter	Blood vessel occlusion and Immunogenicity	Product or process related impurity		None
Container closure integrity	Safety	May be impacted by storage conditions		None

Identity	Safety and efficacy	NA	(b) (4)	None
Appearance Physical Form, Clarity, Color	Safety and efficacy	Manufacturing		None

1. Potency and Strength

Potency is defined relative to a qualified reference standard using a cell based bioassay. The cell based assay acceptance criteria for the DS and DP are (b) (4) (Relative to RS) and on stability. Potency is also tested by a TNFα as described in the DS section above. The DS and DP release and stability acceptance criteria are (b) (4) (Relative to RS). Cyltezo is intended to be marketed as a 40 mg/0.8 ml liquid in a prefilled syringe.

2. Summary of Product Design

Cyltezo is a sterile 50 mg/ml Adalimumab-adbm liquid filled into 1 ml Type (b) (4) glass syringe (b) (4) with a 0.8 ml nominal volume. The syringe is assembled into a prefilled syringe.

3. List of Excipients

Cyltezo excipients include Sodium Acetate Trihydrate (USP, Ph.Eur), Glacial Acetic Acid (USP, Ph.Eur.), Polysorbate 80 (USP, Ph. Eur.) Additional excipient information is located in the Product Quality primary technical review in Panorama.

4. Reference material(s)

The DP reference standard is the Cyltezo (Adalimumab-adbm) drug substance. There is no formal Cyltezo DP reference standard. Cyltezo RS information is located in the DS Product Quality primary technical review in panorama.

5. Manufacturing Process

(b) (4)

(b) (4)

6. Container Closure (CC)

Cyltezo primary CC consists of a 1 ml long pre-filled syringe with a staked needle and rigid needle shield. (b) (4)

(b) (4)

7. DP Stability

The sponsor provided 36 months real time stability results for 9 DP lots and 24 months real time stability data on 3 DP lots to support their proposed 24 month DP expiry. Most stability results are provided for the bare PFS (does not contain finger flange and plungers). One lot of stability results is provided for the fully assembled PFS, and two lots of stability results are provided for the fully assembled PFS (b) (4)

D. Novel Approaches/Precedents: none

E. Product Quality Labeling Recommendations

Cyletzo (adalimumab-adbm is a proposed biosimilar to Humira (adalimumab) and the labeling indicates that:

> *"Cyletzo must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, CYLTEZO may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. CYLTEZO should be discarded if not used within the 14-day period. Record the date when CYLTEZO is first removed from the refrigerator in the spaces provided on the carton* (b) (4) *Do not store CYLTEZO in extreme heat or cold."*

Stability results indicate that the DP will remain stable if during patient use temperature excursions above 77^{o}F occur.

F. Establishment Information

Overall Facility Recommendation: Approve				
Drug Substance				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
Boehringer Ingelheim Fremont, Inc. (BIFI)	6701 Kaiser Drive, Fremont, California 94555	3005925062	Manufacturing of drug substance; Release and Stability testing of drug substance	Approve based on acceptable inspection outcome
		(b) (4)	IPC testing (Mycoplasma, Sterility, In Vitro) of drug substance.	The facility was approved based on acceptable profile

Drug Product				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
Boehringer Ingelheim Fremont, Inc. (BIFI)	6701 Kaiser Drive, Fremont, California 94555	3005925062	Manufacturing, release and stability testing, labelling and packaging of drug product Assembly & labeling of prefilled syringe	Approve based on acceptable inspection outcome
		(b) (4)	Sterility assay (release and stability testing)	The facility was approved based on acceptable profile

G. Facilities

Boehringer Ingelheim Fremont (FEI 3005925062)

A pre-license inspection of the DS and DP manufacturing facility at BIFI was conducted from March 27 – April 4, 2017 by CDER (DIA, DMA, OBP and ORA) in support of BLA 761058 (BI 695501) covering profile codes CBI and SVS. The inspection covered the Quality, Production, Facilities and Equipment, Laboratory Control, and Materials systems. A 10-item FDA-483 was issued. The firm's response to the FDA-483 observations was deemed adequate and the inspection was classified as VAI**.**

H. Lifecycle Knowledge Management

1. Drug Substance

i. **Protocols approved:** Annual stability protocol, qualification of new working reference standard, and protocol for future master and working cell banks.

ii. **Outstanding review issues/residual:** None

iii. **Future inspection points to consider:** None

2. Drug Product

i. **Protocols approved:** Annual stability protocol

ii. **Outstanding review issues/residual:** None

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_____				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-BLA Agreements			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____				
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation	X		
23.		Process		X	
24.		Analytical Methods		X	
25.		Other			
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				

Howard Anderson

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Maria Gutierrez Lugo

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Comments: Proxy for Susan Kirshner

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: July 18, 2017
To: Administrative File, STN 761058/0
From: Ephrem Hunde, Ph.D., Chemical Engineer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu,, Ph.D., Branch 1 Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 2006
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Mfg Facility: Drug Substance: Boehringer Ingelheim Fremont, Inc. (FEI: 3005925062)
Drug Product: Boehringer Ingelheim Fremont, Inc. (FEI: 3005925062)
Cook Pharmica LLC, Bloomington. (FEI 3005949964)
Product: BI 695501 (adalimumab), solution for injection
Dosage: 40 mg/0.8 ml pre-filled syringe
Indication: Rheumatoid arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (PsO)
Due Date: August 26, 2017

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

BLA 761058 was submitted by Boehringer Ingelheim Pharmaceuticals, Inc., which provided information and data to support the manufacture of BI 695501, solution for injection. BI 695501 is a genetically engineered recombinant human monoclonal IgG1 antibody developed as a proposed biosimilar to US-licensed Humira (adalimumab). BI 695501 binds specifically to tumor necrosis factor alpha (TNFα) and neutralizes its biological function by blocking the interaction with the TNF-receptors TNFR1 and TNFR2.

BI 695501 active substance is expressed (b) (4) and produced by cell culture manufacturing process in (b) (4) L scale. BI 695501 is supplied as a sterile solution for injection with strength of 40 mg/0.8 ml (at a concentration of 50 mg/ml) for subcutaneous administration. BI 695501 is a clear to slightly opalescent solution. The drug product is supplied in pre-filled syringes (PFS) (b) (4). The container closure system consists of a 1 mL-long, ready-to-fill, staked needle syringe (b) (4)

(b) (4) plunger stopper and a rigid needle shield. For the PFS final product, the PFS is assembled with an extended finger flange and a plunger rod to enable injection of the drug product.

The subject BLA proposes commercial manufacture of BI 695501 DS and DP at the Boehringer Ingelheim Fremont Inc. facility in Fremont, California (FEI 3005925062), and additional DP manufacturing site at (b) (4) Assembly and secondary packaging of PFS (b) (4) takes place solely at the BIFI. (b) (4) is used as a testing site of the DS and DP.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S.2.1 DS Manufactures

The facilities proposed for BI 695501 (adalimumab) DS manufacturing, and testing are provided in Table 1.

Table 1: Proposed sites for BI 695501 DS manufacturing and testing

Site Name	Address	FEI #	Responsibility
Boehringer Ingelheim Fremont, Inc. (BIFI)	6701 Kaiser Drive, Fremont, California 94555	3005925062	Manufacturing of drug substance; Release and Stability testing of drug substance
(b) (4)			IPC testing (Mycoplasma, Sterility, In Vitro) of drug substance.

Reviewer Comment 1: *The facilities used for commercial manufacturing of BI 695501 drug substance are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**
  - Boehringer Ingelheim Fremont (FEI 3005925062) – DS manufacture and testing facility
    - *Inspection Conducted May 19 – 28, 2014 by SAN-DO* was a GMP surveillance inspection of a bulk drug substance manufacturer covering the Quality, Production, Materials, Facilities and Equipment, and Laboratory Control systems. No FDA-483 was issued and the inspection was classified as NAI.
    - *Inspection Conducted July 18 – August 7, 2012 by SAN-DO* was a GMP surveillance inspection of a bulk drug substance and finished drug product manufacturer covering the Quality, Production, and Laboratory Control systems. No FDA-483 was issued (9 discussion items were indicated in the EIR. The inspection was classified as VAI.
    - *Inspection Conducted February 9 – 25, 2010 by SAN-DO* was a GMP surveillance inspection focusing on the filling/finishing operations for Vectibix (panitumumab) covering the Quality, Production, Facilities and Equipment, and Laboratory Control systems. A 12-item FDA-483 was issued. The inspection was classified as VAI.

Reference ID: 4147957

- [redacted] - Testing Facility
  - *Inspection Conducted* [redacted] *by* [redacted] *DO* was a comprehensive GMP inspection of a control testing laboratory for profile code CTL. Quality, Facilities and Equipment, Materials and Laboratory Controls Systems were covered. No Form FDA 483 was issued at the close of the inspection. The inspection was classified as NAI. The prior two inspections conducted by [redacted] DO on [redacted] and by ORAHQ on [redacted] were both NAI.

- Current Pre-Approval Inspection Decisions
  - Boehringer Ingelheim Fremont (FEI 3005925062) - DS manufacture and testing facility

    A pre-license inspection of the DS and DP manufacturing facility at BIFI was conducted from March 27 – April 4, 2017 by CDER (DIA, DMA and ORA) in support of BLA 761058/0 adalimumab (BI 695501) covering profile codes CBI and SVS. The inspection covered the Quality, Production, Facilities and Equipment, Laboratory Control, and Materials systems. A 10-item FDA-483 was issued. The firm's response to the FDA-483 observations was deemed adequate and the inspection was classified as VAI.
  - [redacted] - Testing Facility

    The facility was approved based on acceptable profile.

Reviewer Comment 2: *The production and testing facilities associated with the manufacture of BI 695501 DS are acceptable from a facilities assessment standpoint.*

3.2.S.2.2 Overview of BI 695501 DS Manufacturing Process at BIFI

BI 695501 is a genetically engineered recombinant human monoclonal IgG1 antibody expressed [redacted]

Reviewer Comment 3: The overview of BI 695501 DS manufacturing operations conducted at Boehringer Ingelheim Fremont, Inc. is adequately described. The BI 695501 DS manufacturing operation was verified during the March 27-April 4, 2017 pre-approval inspection. During the inspection the investigators noted an objectionable condition that raw material control is inadequate. The firm's response to the observation was reviewed and is considered adequate

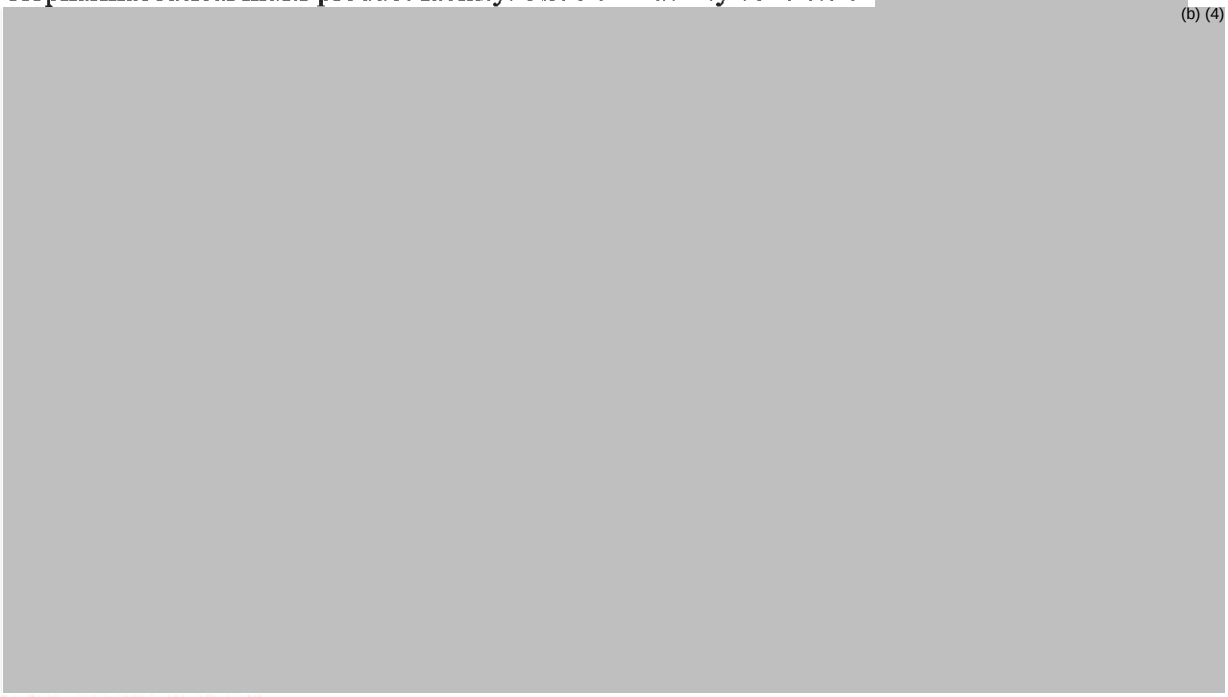
3.2.A.1. FACILITIES AND EQUIPMENT

2. Facility Description (BIFI)

3.1 Facility Design

The Boehringer Ingelheim Fremont, Inc. (BIFI) DS and DP manufacturing facility operates as a biopharmaceutical multi-product facility. The BIFI facility consists of (b) (4)

(b) (4)



Reviewer Comment 4: The Boehringer Ingelheim Fremont, Inc. (BIFI) facility and its security is adequately described and was verified during the March 27-April 4, 2017 pre-approval inspection.

- **2.1 Production, Material, Personnel and Waste Flow**

(b) (4)

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DRUG PRODUCT FACILITIES
3.2.P.1
3.2.P.3.1
The facilities proposed for BI 695501 (adalimumab) DP manufacturing, and testing are provided in Table 6.

TABLE 6: Proposed sites for BI 695501 DP manufacturing and testing

Site Name	Address	FEI #	Responsibility
Boehringer Ingelheim Fremont, Inc. (BIFI)	6701 Kaiser Drive, Fremont, California 94555	3005925062	Manufacturing, release and stability testing, labelling and packaging of drug product Assembly & labeling of prefilled syringe
(b) (4)			Manufacturing, release testing (sterility, subvisible particulates and endotoxin release assays performed), and primary packaging of drug product
			Sterility assay (release and stability testing)

Reviewer Comment 14: *The facilities proposed for commercial manufacturing of BI 695501 drug product are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**
  - Boehringer Ingelheim Fremont (FEI 3005925062) – DP manufacture and testing facility
    - See DS section of this review.
  - (b) (4) DP manufacture and testing facility
    - *Inspection Conducted* (b) (4) by ORAHQ was a GMP surveillance inspection of a human pharmaceutical products and medical devices manufacturer covering the Quality, Production, Laboratory Control, and Facilities and Equipment systems. SVL profile was covered. A 3-item FDA-483 was issued and the inspection was classified as VAI.
    - *Inspection Conducted* (b) (4) by (b) (4) DO was a PAI for two sterile filled parenteral drug products covering the Quality, Production, Laboratory Control, Materials, and Facilities and Equipment systems. A 1-item FDA-483 was issued and the inspection was classified as VAI.
    - *Inspection Conducted* (b) (4) by (b) (4) DO was a surveillance inspection covering the Quality, Production, Materials, and Facilities and Equipment systems. No FDA-483 was issued and the inspection was classified as NAI.
  - (b) (4) Testing facility
    - See DS section of this review.

Reference ID: 4147957

- Current Pre-Approval Inspection Decisions

  - Boehringer Ingelheim Fremont (FEI 3005925062) - DP Manufacture and Testing Facility

    A pre-license inspection of the DS and DP manufacturing facility at BIFI was conducted from March 27 – April 4, 2017 by CDER (DIA, DMA and ORA) in support of BLA 761058/0 adalimumab (BI 695501) covering profile codes CBI and SVS. The inspection covered the Quality, Production, Facilities and Equipment, Laboratory Control, and Materials systems. A 10-item FDA-483 was issued. The firm's response to the FDA-483 observations was deemed adequate and the inspection was classified as VAI.

  - [redacted] (b) (4) DP manufacture and testing Facility

    A pre-license inspection of the DP manufacturing facility at [redacted] (b) (4) was conducted from [redacted] (b) (4) by CDER (DIA and DMA) in support of BLA 761058/0 adalimumab (BI 695501) [redacted] (b) (4) (b) (4) team. The firm provided a written response which included details for acceptable corrective actions which was deemed adequate. The inspection was classified as VAI (downgraded from the initial OAI).

  - [redacted] (b) (4) - Testing Facility

    The facility was approved based on acceptable profile.

Reviewer Comment 14: *The production and testing facilities associated with the manufacture of BI 695501 DP are acceptable from a facilities assessment standpoint.*

3.2.P.3.3 Overview of BI 695501 DP Manufacturing Operations at BIFI

[redacted] (b) (4)

Reference ID: 4147957

A process flow diagram summarizing the BI 695501 DP manufacturing process at BIFI is presented in Figure 1 of Module 3.2.P.3.3 of the submission. Tables of process parameters and process indicator specifications (ranges) are provided for each processing step in Modules 3.2.P.3.3 & 3.2.P.3.4.

Reviewer Comment 15: *The overview of BI 695501 DP manufacturing operations conducted at BIFI is adequately described and was verified during the March 27-April 4, 2017 pre-approval inspection. During the inspection the investigators noted objectionable conditions that include: 1) inadequate quality assurance to invalidate COA, 2) inadequate storage of raw material, 3) failure to thoroughly review a batch failure, and 4) inadequate shipping validation study. The firm's response to the observations was reviewed and is considered adequate.*

3.2.A.1 FACILITIES AND EQUIPMENT (BIFI DP Facility)

- **2.1 Production, Material, Personnel and Waste Flow**

(b) (4)

Reviewer Comment 16: *The BI 596601 DP production, material, personnel and waste flow is adequately described and was verified during the March 27-April 4, 2017 pre-approval inspection.*

4 Drug Product Manufacture

- **4.1 Facility Design of BIFI DP Manufacturing Site**

(b) (4)

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Reference ID: 4147957

CONCLUSION

Adequate descriptions were provided for the facilities proposed for BI 695501 (adalimumab) DS and DP manufacture and testing. The subject BLA is recommended for approval from a facilities assessment perspective.

Ephrem Hunde, Ph.D.
Chemical Engineer
OPF Division of Inspectional Assessment
Branch 1

Ephrem Hunde -S

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Zhihao (Peter) Qiu, Ph.D.
Supervisory Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1 Chief

Zhihao Qiu -S

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