CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125509Orig1s000

CHEMISTRY REVIEW(S)

BLA Standard Submission

Recommendation: Pending resolution of remaining product quality microbiology issues.

BLA125509
Review #1
November 30, 2015

Drug Name/Dosage Form	Anthim® (obiltoxaximab) / Injection
Strength/Potency	600mg/Vial (100 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Indication	Treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.
Applicant/Sponsor	Elusys Therapeutics, Inc.
US agent, if applicable	N/A

A. Names

a. **Proprietary Name:** Anthim

b. **Trade Name:** Anthim®

c. **Non-Proprietary/USAN:** Obiltoxaximab

d. **CAS name:** CAS#1351337-07-9

e. **Common name:** ETI-204

f. **INN Name:** Obiltoxaximab

g. **OBP systematic name:** MAB CHIMERIC (IGG1) (b) (4) [ETI-204]

B. Pharmacologic category: Therapeutic recombinant chimeric DeImmunized™ monoclonal antibody (IgG1) binds to *Bacillus anthracis* protective antigen

Product Overview

Obiltoxaximab (Anthim®) is a chimeric (mouse/human) affinity-enhanced monoclonal antibody of the IgG1κ isotype. Obiltoxaximab binds the free protective antigen domain 4 (PAD4) component of *B. anthracis* toxin and inhibits the binding of protective antigen (PA) to its cellular receptors, and prevents the intracellular entry of the anthrax lethal factor and edema factor; the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance, Drug Product and Immunogenicity	Tao Xie	Division of Biotechnology Review Research II
Facilities	Donald Obenhuber	Division of Inspectional Assessment
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	John Metcalfe	Division of Microbiology Assessment
Business Regulatory Process Manager	Melinda Bauerlien	OPRO/OPQ
Application Technical Lead	Rashmi Rawat	Division of Biotechnology Review Research II

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Jane Dean	OND/DAIP
Cross-disciplinary Team Lead	John Alexander	OND/DAIP
Clinical	Elizabeth O'Shaughnessy Ramya Gopinath	OND/DAIP
Non-Clinical	Amy Nostrandt	OAP/DAIP
Clinical Microbiology	Bala Shukal and Lynette Y. Berkeley	OAP/DAIP
Clinical Pharmacology	Zhixia (Grace) Yan, (K. Bergman, TL)	CDER
Biometrics	Xianbin Li, (Ling Lan, TL)	OB/DBIV

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	DIVISION/OFFICE	e-SIGNATURE
Drug Substance Drug Product	**Tao Xie**	DBRR II/OBP/OPQ	Tao Xie -S 2015.11.30 20:19:29 -05'00'
Microbiology Drug Substance	**Bo Chi**	DMA/OPF/OPQ	Bo Chi -A Digitally signed by Bo Chi -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bo Chi -A, 0.9.2342.19200300.100.1.1=1300194820 Date: 2015.12.01 09:40:10 -05'00'
Microbiology Drug Product	**John Metcalfe**	DMA/OPF/OPQ	John W. Metcalfe -A Digitally signed by John W. Metcalfe -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300198103, cn=John W. Metcalfe -A Date: 2015.12.01 09:48:29 -05'00'
Microbiology Team Leader	**Patricia Hughes**	DMA/OPF/OPQ	Patricia F. Hughestroos t -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroost -S Date: 2015.12.01 10:02:39 -05'00'
Facilities	**Don Obenhuber**	DIA/OPF/OPQ	Donald Obenhuber -A Digitally signed by Donald Obenhuber -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000390000, cn=Donald Obenhuber -A Date: 2015.12.01 07:53:00 -05'00'
Application Technical Lead and Team Leader	**Rashmi Rawat**	DBRRII/OBP/OPQ	Rashmi Rawat -A Digitally signed by Rashmi Rawat -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -A, 0.9.2342.19200300.100.1.1=0014137532 Date: 2015.11.30 16:51:56 -05'00'
Acting Review Chief Product Quality	**Juhong Liu**	DBRRII/OBP/OPQ	Juhong Liu -S Digitally signed by Juhong Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Juhong Liu -S, 0.9.2342.19200300.100.1.1=0010401517 Date: 2015.12.01 10:10:07 -05'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submission Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original BLA submission, BLA125509, eCTD #0000	20 March 2015
Request for proprietary name review, eCTD #0001	01 April 2015
Updated DP manufacturer document, eCTD #0004	29 May 2015
Response to quality questions (IR-1, dated 28May2015), eCTD #0008	17 June 2015
Response to quality questions (IR-2, dated 15June2015), eCTD #0010	30 June 2015
Updated BLA in response to FDA IR-2, eCTD #0016	19 August 2015
Response to quality questions (IR-3, dated 21Aug2015), eCTD #0020	11 September 2015
Extractable evaluation for (b) (4) purification process and (b) (4) validation protocol, eCTD #0022	24 September 2015
Response to quality questions (IR-4, dated 24Sept2015); eCTD #0025	13 October 2015
Update BLA (stability data updates and specification revision), eCTD#0026	20 October 2015
Response to quality questions (IR-6, dated 15Oct2015), eCTD #0030	27 October 2015
Response to quality questions (IR-7, dated 22Oct2015), eCTD seq#0031	27 October 2015
Response to quality questions (IR-8, dated 2Nov2015), eCTD seq#0037	9 November 2015
Response to quality questions (IR-11, dated 13Nov2015), eCTD seq#0039	20 November 2015

B. DMFs:

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Comments
(b) (4)	Type V		(b) (4)	1	adequate	Reviewed in 6/2015 by the reviewer. (b) (4) (b) (4)
(b) (4)	Type III		(b) (4)	3 & 6	adequate	Adequate leachables / extractables information is provided in BLA. DMF was reviewed previously in 1999 (The review is not available in DARRTS).
	Type III			2 & 3	adequate	Adequate leachables / extractables information is provided in BLA. Review in DRRTS 4/17/2009 adequate to be used safely in the (b) (4).
	Type III			3 & 6	adequate	Adequate leachables / extractables information is provided in BLA. This DMF is cross referenced by approved BLA- (b) (4) BLA- (b) (4) DMF was Reviewed previously but the review reports are not available from DARRTS.
	Type III			3 & 6	adequate	Adequate leachables / extractables information is provided in BLA. Review in DRRTS 4/14/2015 adequate to support NADA (b) (4). This MF is cross referenced by approved (b) (4)
	Type V			2	adequate	Review in DRRTS in 2015 adequate for the (b) (4) and (b) (4). No additional review required

(b) (4)	Type III	(b) (4)	2	adequate	Review in DRRTS in 10/20/2009 (b) (4) (b) (4). No review needed. This MF is cross referenced by approved BLA- (b) (4)
	Type III		3 & 2	adequate	Adequate leachables / extractables information is provided in BLA. Reviewed (DRRTS) in 9/25/2012 (b) (4) and adequate to support (b) (4). This MF is cross referenced by approved BLA (b) (4)

[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] Status: 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: *None*

Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

a. Recommendation

A final recommendation from the Office of Pharmaceutical Quality, CDER, for STN 125509 Anthim (obiltoxaximab) manufactured by Elusys Therapeutic Inc. is pending due to 1) outstanding requests for information from Division of Microbiology assessment (DMA), regarding the ability of the USP BET methods to detect endotoxin (RSE/CSE) spiked into the (b) (4) drug substance and formulated drug product; and 2) the final classification of compliance status of manufacturing site Lonza, Portsmouth, USA is still pending.

There are no outstanding product quality issues from OBP perspective. A final recommendation will be provided in an addendum to this review.

b. Benefit/Risk Considerations

The obiltoxaximab is a chimeric antibody that targets anthrax protective antigen (PA). The mechanism of action is based on its ability to neutralize the lethal toxin mediated cytotoxicity. The DS and DP manufacturing process are well controlled and capable of producing product of consistent quality with the exception of the DS and DP endotoxin testing issue related to the endotoxin recovery assessment in the product formulation. Therefore the review of the microbiological control for the DS and DP manufacturing process is currently incomplete because we are waiting for the applicant to respond to information requests.

There are some minor product quality issues identified during the BLA review, which do not preclude approval of the BLA and will be addressed as post marketing commitments.

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

1. Develop reduced and non-reduced SDS-based assays capable of providing quantitative data for the evaluation of size related product impurities and implement these assays in the release and stability program for obiltoxaximab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. Provide the analytical procedure, validation report, proposed acceptance criteria, and data used to set the proposed acceptance criteria.

2. Conduct validation studies to confirm the shipper is suitable for maintaining critical quality attributes during shipping of obiltoxaximab drug product. This should include consideration for worst case shipping routes. The study will include monitoring of temperature during the shipment, as well as testing of pre- and post- shipping samples of obiltoxaximab drug product quality (e.g., appearance, protein concentration, purity by SEC-HPLC, reduced and non-reduced SDS-PAGE, icIEF, visible and sub-visible particulates and potency).

3. Conduct a study to confirm compatibility of the drug product with syringe infusion components used for administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, icIEF, visible and sub-visible particulates; and potency. Conduct a study to support the worst case cumulative hold times in obiltoxaximab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoxaximab DS. These data are expected to demonstrate that there is no adverse impact to product quality when the manufacturing of a DS batch involves (b) (4)

4. Re-evaluate obiltoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. Proposed changes to the specifications will be provided in the final report.

5. Re-evaluate obiltoxaximab drug product lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. (b) (4)

6. Establish a permanent control limit for (b) (4) of production (b) (4) and (b) (4), of (b) (4) unit operations after (b) (4) control points have been analyzed. The (b) (4) limits and supportive data should be submitted in the annual report.

7. (b) (4)

8. Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL).

9. Re-evaluate and establish final (b) (4) bioburden and endotoxin limits for all the sampling points after ten commercial lots have been manufactured.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below provides a summary of product related critical quality attributes that are relevant to both drug substance and drug product. The table includes the identification of the various attributes along with their risk management. For additional information see Appendix A for the OBP product quality review and Appendix B for the product quality microbiology review.

Identification of other CQAs specific to drug substance (e.g., process related impurities, adventitious agents, pH, appearance, etc.) or drug product are described in separate risk tables in section B, Drug Substance Quality Summary and section C, Drug Product Quality Summary.

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

CQA	Risk	Origin	Control Strategy	Other
(b) (4)				

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

a. Description: Obiltoxaximab is a chimeric affinity-enhanced monoclonal antibody (mAb) of the IgG1κ isotype that binds the PA component of *B. anthracis toxin*. Obiltoxaximab has a molecular weight of approximately 148 kDa. Obiltoxaximab is produced via cultures of (b) (4) murine GS-NS0 myeloma cells.

b. Mechanism of action: Obiltoxaximab binds free PA with an affinity equilibrium dissociation constant (Kd) of 0.33 nM, and inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax lethal factor and edema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

c. Potency Assay: The biological activity of obiltoxaximab is determined by two methods. An ELISA based antigen binding assay PAA3 that measures the functional binding activity of obiltoxaximab and a cell-based bioassay Lethal Neutralization Assay (LNA) that measures neutralization of lethal-toxin mediated cytotoxicity.

d. Reference material(s): The current reference material (b) (4) was produced from (b) (4) The sponsor commits to implement (b) (4)

e. Critical starting materials or intermediates: (b) (4)

Cell Banks: Obiltoxaximab is produced from a recombinant DNA-derived murine myeloma cell line (NS0) using standard cell culture techniques. The obiltoxaximab antibody was engineered from the murine monoclonal antibody (14B7) gene sequences (H and L chain sequences) originally developed by the United States Army Medical Research Institute for Infectious Diseases (USAMRIID). Elusys obtained the original 14B7 hybridoma from NIH under a Cooperative Research and Development Agreement (CRADA) with USAMRIID. The manufacturing cell line (b) (4) for the production of ETI-204 was developed by Elusys under contract with (b) (4) DNA sequence in variable regions on both the heavy and light chains of obiltoxaximab gene have been manipulated to eliminate potential immunogenic murine sequences and enhance the affinity of the antibody for its target. The sequence coding Fc region is from human. The recombinant obiltoxaximab gene is expressed using Glutamine Synthase (GS) Expression System.

(b) (4)

f. Manufacturing process summary: Obiltoxaximab is manufactured at Lonza Biologics NH, USA using standard monoclonal antibody manufacturing process. (b) (4)

[redacted]

An adequate microbial control strategy is in place for the drug substance manufacturing process. [redacted] Bioburden and endotoxin are monitored [redacted] However, studies to confirm the validity of the endotoxin release test to detect spiked endotoxin is pending.

(See Appendix A and B for more information)

g. Container closure: The container closure system (CCS) for obiltoxaximab BDS is a [redacted]. A proprietary extractable study has been conducted on the DS container closure system to demonstrate that the [redacted] for obiltoxaximab is safe and acceptable for storage of the BDS at the recommended storage conditions.

h. Dating period and storage conditions: The data provided in the BLA support a shelf of [redacted] months for obiltoxaximab drug substance when stored [redacted] °C.

The post-approval stability protocols and commitment to place [redacted] DS [redacted] each year (with production) on stability protocols are provided and found to be acceptable.

C. Drug Product [Anthim] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs:

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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)	
Endotoxin	Safety	Contaminants could be introduced throughout DP manufacturing or due to integrity failure of the container closure.		
Particulate matter (sub-visible)	Safety and Immunogenicity	Sub-visible particulates could form throughout manufacturing or on storage. Might contain product- and process- related impurities		
Appearance - Visible particulates	Safety and efficacy	Visible particulate might be impacted by the manufacturing process and storage conditions		
Appearance – Color, Clarity and degree of opalascence	Safety and efficacy	Manufacturing process, formulation, and storage conditions		
pH	Safety and efficacy	pH is most likely impacted by formulation and compounding. No change on stability is expected.		

Osmolality	Safety	Osmolality is most likely impacted by formulation and compounding. No change is expected on stability.	(b) (4)	
Polysorbate 80	Safety and efficacy	Level of Polysorbate 80 excipient is impacted by formulation and compounding. No changes are expected on stability.		
Protein Concentration	Safety and efficacy	Protein concentration would be impacted by formulation and compounding. Might be impacted by storage conditions		
Identity	Safety and efficacy	General CQA		
Container closure integrity	Safety	CQA, Might be impacted by storage conditions		
Leachables/extractables	Safety	Process-related leachables and extractables could potentially be introduced by any product contact equipment, containers and consumables.		

a. Potency and Strength: Anthim is supplied as 600 mg/6 mL (100 mg/mL) solution in single-dose vials for intravenous injection.

b. Description/Commercial Image: Anthim is a clear to opalescent, colorless to pale yellow to pale brownish-yellow solution and may contain few translucent-to-white proteinaceous particulates. Anthim is provided in sterile, (b) (4) mL type 1 glass vial with (b) (4) rubber stopper (gray) and an aluminum seal with (b) (4) flip-off cap (b) (4)

c. List of Excipients: Each mL of Anthim contains 6.2 mg of L-histidine, (b) mg of polysorbate 80, 36 mg of sorbitol. (b) (4) pH to 5.5.

d. Reference material(s): Same as drug substance

e. Manufacturing Process: (b) (4)

f. Container Closure: The container closure system for Anthim drug product includes vial, stopper and seal. The vial is a (b) (4) mL Type 1 glass ((b) (4)

g. Expiration Date & Storage Conditions: The stability data in the BLA support a shelf life of 18 months for Anthim drug products when stored at 5 ±3°C.

h. List of co-packaged components: N/A

D. Novel Approaches/Precedents

None

E. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C

Do note freeze

Protect from light

Do not shake

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
Function	**Site Information**	**Duns/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
Manufacture of ETI-204 BDS In-Process testing, except for those tests performed by: (b) (4) ((b) (4) Sample Testing) • Release testing -Appearance, protein concentration, osmolality, pH, icIEF, reduced and non-reduced SDS-PAGE, SE-HPLC, host cell DNA by qPCR, Protein A ELISA, host cell protein ELISA, bioburden and endotoxin • Stability testing - Appearance, protein concentration, pH, icIEF, reduced and non-reduced SDS-PAGE and SE-HPLC • Alternate release and stability testing - PAA3 ELISA	(b) (4)				Pending
(b) (4) Sample Testing: Mycoplasma					Approved

	(b) (4)	
• (b) (4) Sample Testing: - 28 Day In-vitro virus assay • (b) (4)		Approved

	(b) (4)	
• Release and stability testing: PAA3 ELISA		Approved
• Release testing: Polysorbate 80		Approved

	(b) (4)	
• Release testing: -Lethal Toxin Neutralization Assay (LNA) • Stability testing: -LNA • For information only- release testing -Reduced and non-reduced CESDS		Approved
DRUG PRODUCT		
Function	(b) (4)	**Final Recommendation**
• Fill and Finish of ETI-204 DP - Identity test of incoming bulk drug substance (SDS-PAGE) - In-process testing • Release Testing - protein concentration - visible particulates • Packaging and Labeling		Approved
• Release testing - Appearance, pH, osmolality,		Pending

imaged capillary isoelectric focusing (icIEF), reduced and non-reduced SDS-PAGE, size-exclusion HPLC (SE-HPLC) and endotoxin • Stability testing - Appearance, protein concentration, pH, icIEF, reduced and non-reduced SDS-PAGE, SE-HPLC, endotoxin and particulate matter • Alternate release and stability testing: -PAA3 ELISA	(b) (4)	
• Release and stability testing - PAA3 ELISA		Approved
Excipient Release Testing - Polysorbate 80		
• Release testing - Sterility - Particulates		Approved

	(b) (4)	
• Release and stability testing - Lethal Toxin Neutralization Assay (LNA) • For information only- release and stability testing - Reduced and non-reduced capillary electrophoresis SDS (CE-SDS)		Approved
• Stability Testing - Helium leak test (container closure		Approved

integrity)	(b) (4)	
Repacking and labeling at the Strategic National Stockpile (SNS)		Approved

G. Lifecycle Knowledge Management

B. Drug Substance

a. Protocols approved: Annual GMP stability protocol, stability protocols for the extension of shelf life, reprocessing protocols for (b) (4)

b. Outstanding review issues/residual risk: None

c. Future inspection points to consider: Follow up on 483 citations

C. Drug Product

a. Protocols approved: Annual GMP stability protocol and Stability protocols for the extension of shelf life

b. Outstanding review issues/residual risk: See PMCs

c. Future inspection points to consider: Follow up on 483 citations

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-NDA Agreements tem)			
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.	Design Space – Process		X	
24.	Design Space – Analytical Methods		X	
25.	Design Space – Other		X	
26.	Other QbD Elements			
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 _____				

BLA STN 125509

OBILTOXAXIMAB (Anthim®)

Elusys Therapeutics, Inc.

Product Quality Reviewer: Tao Xie, Ph.D

Team Leader and ATL: Rashmi Rawat, Ph.D

Division of Biotechnology Research and Review II
Office of Biotechnology Products, OPQ

OBP CMC Review Data Sheet

1. **BLA#:** STN125509

2. **Review Date:** November 23, 2015

3. **Primary Review Team:**
CDTL: John Alexander
Medical officer: Elizabeth O'Shaughnessy and Ramya Gopinath
Pharm/Tox: Amy Nostrandt (Wendelyn Schmidt, TL)
Application Technical Lead (ATL): Rashmi Rawat
Product quality reviewer: Tao Xie (Rashmi Rawat, TL)
Product quality-Microbiology drug substance: Bo Chi (Patricia Hughes, TL)
Product quality-Microbiology drug product: John Metcalfe (Patricia Hughes, TL)
CMC labelling reviewer: Jibril Abdus-Samad
Facilities: Donald Obenhuber
Clinical microbiology:Shukal Bala and Lynette Berkeley (Kerry Snow, TL)
Clinical pharmacology: Zhixia (Grace) Yan (Kimberly Bergman, TL)
Statistics: Xianbin Li and Ling Lan (Karen Higgins, TL)
Product quality RPM: Melinda Bauerlien
OND RPM: Jane Dean

4. **Major 21st Century Review Deadlines**
Filing Meeting: May 11, 2015
Mid-Cycle Meeting: September 1, 2015
Late-Cycle Meeting: December 11, 2015
Wrap-Up Meeting: January 29, 2016
Primary Review Due: November 23, 2015
Product Quality ATL Executive Summary Due: November 30, 2015
CDTL Memo Due: February 5, 2015
PDUFA Action Date: March 18, 2016

5. **Communications with Sponsor and OND**

Communication/Document	Dated
Pre-BLA Meeting (include CMC)	July 30, 2013
Filing communication	May 22, 2015
Quality information request (IR)-1	May 28, 2015
Quality information request (IR)-2	June 15, 2015
Quality information request (IR)-3	August 21, 2015
Quality information request (IR)-4	September 24, 2015
Quality information request (IR)-6	October 15, 2015
Tele-conference with Elusys	October 19, 2015

Quality information request (IR)-7	October 22, 2015
Quality information request (IR)-8	November 2, 2015
Quality information request (IR)-11	November 13, 2015

6. Submission(s) Reviewed

Submission	Date Received	Review (Yes/No)
Original BLA submission, BLA125509, eCTD #0000	20 March 2015	Yes
Request for proprietary name review, eCTD #0001	01 April 2015	Yes
Updated DP manufacturer document, eCTD #0004	29 May 2015	Yes
Response to quality questions (IR)-1, eCTD #0008	17 June 2015	Yes
Response to quality questions (IR)-2, eCTD #0010	30 June 2015	Yes
Updated BLA in response to FDA IR-2, eCTD #0016	19 August 2015	Yes
Response to quality questions (IR)-3, eCTD #0020	11 September 2015	Yes
Extractable evaluation for (b) (4) purification process and (b) (4) validation protocol, eCTD #0022	24 September 2015	Yes
Response to quality questions (IR)-4, eCTD #0025	13 October 2015	Yes
Update BLA (stability data updates and specification revision), eCTD#0026	20 October 2015	Yes
Response to quality questions (IR)-6, eCTD #0030	27 October 2015	Yes
Response to quality questions (IR)-7, eCTD #0031	27 October 2015	Yes
Response to quality questions (IR)-8, eCTD #0037	13 November 2015	Yes
Response to quality questions (IR)-11, eCTD #0039	20 November 2015	Yes

7. Drug Product Name/Code/Type

a. **Proprietary Name**: Anthim

b. **Trade Name**: Anthim®

c. **Non-Proprietary/USAN**: Obiltoxaximab

d. **CAS Name**: Immunoglobin G_1, anti - (*Bacillus anthracis* anthrax protective antigen) (human-Mus musculus monoclonal ETI-204 heavy chain), disulfide with human-Mus musculus monoclonal ETI-204 κ-chain, dimer. (CAS#1351337-07-9)

e. **Common Name**: ETI-204

f. **INN Name**: Obiltoxaximab

g. **Compendial Name**: N/A

h. **OBP Systematic Name**: MAB CHIMERIC (IGG1) (b) (4) [ETI-204]

i. **Other Names**: ETI-204, (b) (4) mAb

8. Pharmacological Category:

chimeric DeImmunized™ monoclonal antibody (IgG_1) binds to *Bacillus anthracis* protective antigen.

9. Dosage Form:

Injection: 600 mg/6 mL (100 mg/mL) solution in single - dose vial

10. Strength/Potency

(i) The concentration/strength of the Drug Product: Anthim (obiltoxaximab, ETI-204) drug product is supplied as liquid formulation in single-use vials. Each vial contains 6 mL 100 mg/mL obiltoxaximab.

(ii) Type of potency assay (s): The biological activity of obiltoxaximab is determined by two methods. An antigen binding ELISA assay (PAA3) measures the functional binding activity of obiltoxaximab and a cell-based bioassay Lethal Neutralization Assay (LNA) measures neutralization of lethal-toxin mediated cytotoxicity.

11. Route of Administration: IV

12. Referenced Master Files:

DMF #	Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Provided	Deferred to clinical/nonclinical review teams
			Provided	The MF (b) (4) is reviewed. The information is sufficient to support the BLA. This file was also reviewed during review of BLA (b) (4) and determined to be adequate.
			Provided	DMF was reviewed previously in 1999 (this review is not available from DARRTS). Adequate leachables/extractables information is provided in BLA. Cross referenced by pending BLA (b) (4), approved NDA-(b) (4)
			Provided	Review in DRRTS 4/17/2009 adequate to be used safely in the (b) (4) Adequate leachables/extractables information is provided in BLA. This MF is cross referenced by approved BLA-(b) (4). No review required.
			Provided	DMF was Reviewed previously but the review reports are not available from DARRTS. Adequate leachables/extractables information of the CCS of the DP is provided in BLA. This MF is cross referenced by approved BLA-(b) (4) No review required.
			Provided	Review in DRRTS 4/14/2015 adequate to support NADA (b) (4). Adequate leachables/extractables information for the (b) (4) of DP is provided in BLA. This MF is cross referenced by approved BLA (b) (4)

				No additional review required
[redacted]			Provided	Review in DRRTS in 2015 adequate for the [redacted] and [redacted] process. No additional review required
			Provided	Review in DRRTS in 10/20/2009 The container integrity testing information is adequate. No review needed. This MF is cross referenced by approved BLA- [redacted]
			Provided	Review in DRRTS in 9/25/2012 meet 21 CFR314.70(b) and adequate to support [redacted] leachables/extractables information of the [redacted] of the DP is provided in BLA. This MF is cross referenced by approved BLA [redacted] No review required

Inspectional Activities

A pre-license inspection of the drug substance manufacturing facility at Lonza Biologics Inc., Portsmouth, NH was conducted on [redacted] following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, under FACTS assignment # [redacted]. The inspection was conducted to support the approval of Elusys' BLA STN125509/0 for obiltoxaximab (Lonza code 5069) and [redacted] The inspection was system-based and covered Quality, Facilities and Equipment, Production, Materials, and Laboratory systems. The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products; CP 7346.832, Pre-Approval Inspections/Investigations; and ICH Q7. This inspection was limited to the manufacturing of obiltoxaximab and [redacted].

A seven-item Form FDA 483 was issued to the firm at the end of the inspection on [redacted] with the following observation summaries:

1) The risk assessment to justify procedure controls and process containment that are necessary to prevent cross-contamination of [redacted] and 5069 (Lonza code for obiltoxaximab) drug substances by a potent product is inadequate.

2) No specific [redacted] to process final drug substance bulk is specified in [redacted] and 5069 (Lonza codes) drug substance batch records [redacted] and USPO-9921, respectively.

3) Batch record [redacted] step of the 5069 (Lonza code) drug substance manufacturing process is inadequate in that it does not instruct operators to avoid [redacted].

4) There are deficiencies in deviation handling.

5) Procedure USPO-6144, "Data Recording and Review in Quality Control" for investigating invalid assays for QC release and stability test methods is inadequate.

6) There are insufficient verification data at scale for the effectiveness of the sanitization and storage solutions for the [redacted] (b) (4) used for [redacted] (b) (4) and 5069 (Lonza codes) drug substance manufacturing processes.

7) Equipment cleaning validation for [redacted] (b) (4) and 5069 (Lonza codes) drug substance manufacturing processes is inadequate.

14. Consults Requested by OBP

None

15. Quality by Design Elements

Process development studies for obiltoxaximab used risk assessment and design of experiment elements to optimize manufacturing process.

16. Precedents

There are no precedents set by the review of this application.

17. Administrative

A. Signature Block

Name and Title	Signature and Date
Tao Xie, Ph.D. Product Quality Reviewer, DBRRII/OBP	Tao Xie -S Digitally signed by Tao Xie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tao Xie -S, 0.9.2342.19200300.100.1.1=0011466376 Date: 2015.11.23 15:22:04 -05'00'
Rashmi Rawat, Ph.D. Team Leader, DBRRII/OBP	Rashmi Rawat -S Digitally signed by Rashmi Rawat -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -S, 0.9.2342.19200300.100.1.1=0014137532 Date: 2015.11.23 15:29:29 -05'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this BLA support the conclusion that the manufacture of Anthim (obiltoxaximab, ETI-204) 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 multiple production runs at both drug substance and drug product manufacturing sites.

We recommend that Anthim (obiltoxaximab) be approved for human use (under conditions specified in the package insert) from OBP product quality perspective.

We recommend an expiry period of (b) (4) months for obiltoxaximab drug substance when stored at (b) (4) °C.

We recommend an expiry period of 18 months for Anthim drug product when stored at 5±3°C.

The stability protocols are acceptable and extension of expiry based on additional real time stability data can be reported to the BLA in an Annual Report.

II. List of Deficiencies To Be Communicated

None

III. List of Post-Marketing Commitments/Requirement

We recommend the following seven PMCs:

1. Develop reduced and non-reduced SDS-based assays that are capable of providing quantitative data for the evaluation of size related product impurities and implement these assays in the release and stability program for obiltoxaximab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. Provide the analytical procedure, validation report, proposed acceptance criteria, and data used to set the proposed acceptance criteria.
2. Conduct validation studies to confirm acceptable product quality and shipper performance during shipping of obiltoxaximab drug product. This should include consideration for worst case shipping routes including routes to testing sites. The study will include monitoring of temperature during the shipment, as well as testing of pre- and post- shipping samples of obiltoxaximab for drug product quality (e.g., appearance, protein concentration, purity by SEC-HPLC, reduced and non-reduced SDS-PAGE, icIEF, visible and sub-visible particulates and potency) (b) (4)
3. Conduct a study to confirm compatibility of the drug product with syringe infusion components used for administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, visible and sub-visible particulates; and potency. (b) (4)

4. Conduct a study to support the worst case cumulative hold times in obiltoxaximab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoxaximab DS. These data are expected to demonstrate that there is no adverse impact to product quality when the manufacturing of a DS batch involves (b) (4)
5. Re-evaluate obiltoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. (b) (4)
6. Re-evaluate obiltoxaximab drug product lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. (b) (4).
7. Provide a commitment to establish a permanent control limit for (b) (4) of production (b) (4) and (b) (4) of (b) (4) unit operations after (b) (4) points have been analyzed. The (b) (4) limits and supportive data will be submitted in the annual report.

IV. Review of Common Technical Document-Quality Module 1

A. Environment Assessment or Claim of Categorical Exclusion

Elusys Therapeutics, Inc. claims a categorical exclusion from the requirement of an Environmental Assessment in accordance with 21 CFR 25.31 (c). "No extraordinary circumstance exists" is stated per 21 CFR 25.15 (d).

Reviewer's Comment: *The claim of categorical exclusion is deemed acceptable.*

V. Primary Container Labeling Review

The proposed Anthim commercial and Strategic National Stockpile (SNS) product is a single-use vial in an individual carton containing a package insert. (b) (4)

Reviewer's Comment: *The container labels and carton labeling are reviewed by OBP labelling reviewer Jibril Abdus-Samad.*

VI. Review of Common Technical Document-Quality Module 3.2

Obiltoxaximab (Anthim®) is a chimeric affinity-enhanced monoclonal antibody (mAb) of the IgG1κ isotype. Obiltoxaximab binds the free PA component of *B. anthracis* toxin and inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax lethal factor and edema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

Obiltoxaximab has a molecular weight of approximately 148 kDa and binds the free PA with an affinity equilibrium dissociation constant (Kd) of 0.33 nM. Obiltoxaximab is produced from a recombinant DNA-derived murine myeloma cell line (GS-NS0) using standard cell culture techniques. The obiltoxaximab antibody was engineered from the murine monoclonal antibody (14B7) gene sequences (H and L chain sequences) originally developed by the United States

Army Medical Research Institute for Infectious Diseases (USAMRIID). DNA sequence in variable regions on both the heave and light chains of obiltoxaximab gene have been manipulated to eliminate potential immunogenic murine sequences and enhance the affinity of the antibody for its target. The sequence coding Fc region is from human. The recombinant obiltoxaximab gene is expressed using Glutamine Synthetase (GS) Expression System.

Obiltoxaximab drug substance is manufactured at Lonza Biologics, Portsmouth, NH. The manufacturing process starts (b) (4)

Anthim drug product is formulated as 100 mg/mL obiltoxaximab in (b) (4) 40 mM histidine, 200 mM sorbitol, pH 5.5, 0.01% polysorbate 80. The formulation of DP is the same as obiltoxaximab (b) (4). Anthim drug product is supplied in a sterile, (b) (4) glass, single-dose vial, containing 600mg/6 mL of obiltoxaximab.

Anthim drug product is filled and finished at (b) (4). For manufacture of the DP, (b) (4)

VII. Review of Immunogenicity Assays-Module 5.3.1.4

To detect anti-drug antibody (ADA) a tiered approach ECL-based binding antibody assay is used that includes initial screening assay followed by confirmatory assay and titration of the samples that were found confirmed positive. The sensitivity of the screening assay was determined to be 27ng/mL. A sample containing 500 ng/mL surrogate ADA is shown to detect antibodies to drug in the presence of obiltoxaximab levels of up to 50µg/mL. This response is generally considered clinically meaningful. Overall, the ADA screening assay is considered to be suitable for the intended use. The sponsor also developed a cell-based assay to detect neutralizing antibody

(NAb assay) response to obiltoxaximab. However, this assay was found to be very sensitive to the presence of drug in the patients' samples. The tolerance of the NAb assay for obiltoxaximab was shown to be approximately 1000 ng/mL and 500ng/mL for high ADA and low ADA positive controls. These levels are below obiltoxaximab serum concentration that is expected to be present in the patients' immunogenicity samples. Therefore this assay is not considered suitable for the intended use. After consulting with the clinical pharmacology discipline reviewer it was determined that it is acceptable because a) this product is given as a single dose; b) the ADA response is only detected in 3% of clinical study population; and c) the presence of ADA do not appear to have any discernable effect on obiltoxaximab PK following IV administration. Based on this risk assessment and evaluation it was concluded that the risk of developing the neutralizing antibody are minimal for this product.

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(b) (4)

3.2.P.5.2 And 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer's Comments: *Analytic methods to be used in testing of both obiltoxaximab drug substance and drug product release and stability include the appearance, osmolality, pH, polysorbate 80, icIEF, reduced and non-reduced SDS PAGE, reduced and non-reduced CE-SDS, SE-HPLC (gel permeation HPLC), PAA3, LAN and LAL assays. The procedures and qualification information of these methods are reviewed in Section 3.2.S.4.2 and 3.2.S.4.3. The drug product specific assays are 1) protein concentration assay cSOP-0221 for DP release, to be assayed at the* (b) (4)*, 2) The particulate matter and sterility methods, both methods confirm to USP. The two methods will be performed at* (b) (4)*, contracted and on behalf of* (b) (4)*.*

Protein concentration method cSOP-0221 at (b) (4)

The (b) (4) method cSOP-0221 uses UV spectrophotometer to determine obiltoxaximab Drug Product protein concentration. The extinction coefficient used for obiltoxaximab is (b) (4). (b) (4)

(b) (4)

Reviewer's Comments: *The cSOP-0221 assay is deemed to be validated for its intended use.*

Particulates Matter methods

For the drug Product release, the visible particulates test (USP<1>) is performed by (b) (4) inspectors based on ANSI/ASQZ1.4. For a typical lot size (b) (4) vials, (b) (4) vials are pulled for (b) (4) inspection, of which no more than (b) (4) vials may have particulates (Table II-B of the American Society for Quality, single sampling plan for tightened inspection). There is no analytical method for this inspection. According to the sponsor (response to IR-11) the acceptance criteria for the visible particulates for the release is "essentially free of particulates" as per USP<1>.

The visible particulates test in drug product stability program is conduct at (b) (4) using (b) (4). This (b) (4) method conforms to EP 2.9.20. (b) (4)

The subvisible particulate matter for SP release is assayed by (b) (4). The specification for the obiltoxaximab DP meets the USP <788> specification for small volume containers (≥10µm: (b) (4) particles/container and ≥25µm: (b) (4) particles/container). BLA provides a validation report 14-VR-291 that qualified both USP<788> Particulate Matter and USA <71> Sterility for testing obiltoxaximab drug product at (b) (4).

Subvisible particulates matter is tested per (b) (4) Light Obscuration Method using HIAC Royco Liquid Particulate Counting System (LPC) model #9703. (b) (4)

(b) (4)

The qualification of the assay is performed to demonstrate the successful completion of particulate matter method to be used ETI-204 samples. Samples from three obiltoxaximab DP PV lots were tested using (b) (4). All prior set forth acceptance criteria were met. There were no deviations encountered during the qualification

Reviewer's Comment*: The (b) (4) particulate matter method is deemed qualified and may be used for analysis of obiltoxaximab drug product. Review of the methods of Endotoxin, Sterility and helium leak test: are deferred to DMA review team.*

3.2.P.5.4 Batch Analyses

Three cGMP engineering lots of obiltoxaximab DP, 3-FIN-1512, 3-FIN-1513, 3-FIN-1514 were manufactured at (b) (4) using Lonza DS lots. Another three cGMP process validation (PV) batches, 3-FIN-1702, 3-FIN-1703 and 3-FIN-1704 were manufactured for the purpose of validation of formulation and filling process. The DS materials used for production of the PV batches were from (b) (4) DS PV lots manufactured at Lonza. All engineering and PV lots met the current DP specification at the time of release. Release data obiltoxaximab DP lots are summarized in section P5.4 of the BLA.

Manufacturing history of obiltoxaximab DP batches presented in table below is derived from the submission by the CMC reviewer. The batches with red numbers are DP materials that were used in the clinical and nonclinical studies during the IND stage. Those lot numbers within the brackets are sources of DS used for manufacturing the DP batch.

Obiltoxaximab Drug Product Manufacturing History

(b) (4)

Reviewer's Comment: *The batch analysis data provided for all The DP batches produced to date are acceptable.*

P.5.6 Justification of Specifications [Obiltoxaximab, 100 mg/mL Vial]

The current DP release specifications are used historically for release clinical material. The specifications for the DP release and stability are the same as those for DS release and stability with the exception of

a. Protein concentration that has different acceptance criteria because of the difference between the BDS and FDP (b) (4).
b. The DP control also include test for visible and
c. Subvisible particulates
d. Sterility and Endotoxin

Tests and specifications common in testing for both drug product and drug substance are summarized in table presented in section S.4 in the review. The justification of specifications for the drug product specific tests is summarized below:

a) Protein Concentration

The specification has been narrowed from original 100± (b) (4) mg/mL to 100± (b) (4) mg/mL. Protein concentration within ± (b) (4) % range is more appropriate. The release data and observation in stability also support this revision.

b) Appearance – visible particulates

The specification is revised to define the specification for release and for stability. The revised specification supported by following data:

- (b) (4)

c) Particulate Matter

Specification for ≥ 10µm is (b) (4) /container, the following data are observation in DP lots release data and stability.

- (b) (4)

Specification for ≥25µm is (b) (4) /container. The following data are observation in DP lots release data and stability.

- (b) (4)

d) Endotoin (LAL) < (b) (4) EU/mg and sterility (b) (4) both are appropriate.

Reviewer's Comment*: Based on our analysis of the stability data, batch analysis and the release data of the batches were used in the non-clinical and clinical studies some of the proposed specifications were not acceptable as identified in the table above. The sponsor was asked to*

revise the specifications for those tests. The sponsor agreed with the suggested revisions and updated the DP release and stability specifications.

The Sponsor states that the specifications will be reevaluated after a total of (b) (4) lots of BDS have been manufactured using the full scale BDS commercial process. ***Reviewer's Comments:*** *A PMC is recommended: Re-evaluate obiltoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, corresponding data, analysis, and statistical plan used to evaluate the specifications.* (b) (4) *t.*

3.2.P.6 Reference Standards or Materials

Reviewer's Comment: *The reference standard for obiltoxaximab DP release and stability is the same as that used for DS release and stability. The reference standard information is reviewed in section 3.2.S.5.*

3.2.P.7 Container Closure System

The primary packaging of obiltoxaximab FDP includes vial, stopper and seal. The vial is a (b) (4) mL Type 1 glass (b) (4) with a 20 mm opening. The vial is manufactured by (b) (4) (USP/NF grade). The fill level to the base of the neck of the vial is approximately (b) (4) mL.

Table 1: Container-Closure System

Description of Container and Components	Materials of Construction	Handling	Specification
Vial, (b) (4) mL, 20 mm opening	Type 1 Glass (b) (4) Vial	(b) (4)	USP/NF
Rubber Stopper, 20 mm	(b) (4)		USP/NF
Seal, 20 mm			NA

NA - Not Applicable

The stopper is a 20 mm, (b) (4) stopper manufactured and distributed by (b) (4) (USP/NF grade). The stopper has (b) (4) .

The seal is a 20 mm (b) (4) Flip-Off (b) (4) over seal manufactured and distributed by (b) (4)

Secondary Packaging: For the commercial package, each vial will be contained in an individual carton that protects the DP from potential sources of light during long term storage.

Reviewer's Comments: *Materials of the glass vial of obiltoxaximab FDP CCS are commonly used for antibody products. Drug Master Files contain information for the composition, specification and tests of the CCS components are provided. Container closure integrity test is checked in the stability of the three PV lots. A stability study to evaluate leachates in Anthim DP vials is ongoing under real time storage conditions.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary

Stability of Registration Drug Product lots

There are four obiltoxaximab drug product registration lots that are current on stability program. All these DP lots are filled and finished at (b) (4) facility using commercial manufacturing process. DP Lot 3-FIN-1512 is an engineering lot which contains BDS from Lonza commercial scale production prior to PV runs. The other three lots (3-FIN-1702, 3-FIN-1703, and 3-FIN-1704) are from the DP PV runs and obiltoxaximab BDS from Lonza drug substance PV lots were used to manufacture the DP process validation lots. The process for the engineering lot and the process of PV runs are similar and there is no process parameter changes specified. The storage conditions and lots placed on stability are outlined in Table 1.

Table 1: ETI-204 DP Validation Lots – Storage Conditions

ETI-204 DP Lot	Storage Conditions
3-FIN-1512	-20°C ± 5°C (-20°C) Upright
	5°C ± 3°C (5°C) Upright
	25°C ± 2°C/60 ± 5% Relative Humidity (25°C/60% RH) Upright
3-FIN-1702	5°C Upright
	25°C/60% RH Upright

Table 1: ETI-204 DP Validation Lots – Storage Conditions (Continued)

ETI-204 DP Lot	Storage Conditions
3-FIN-1703	5°C Upright
	5°C Inverted
	25°C/60% RH Upright
	25°C/60% RH Inverted
3-FIN-1704	5°C Upright
	5°C Inverted
	25°C/60% RH Upright
	25°C/60% RH Inverted

The engineering lot 3-FIN-1512 is being tested on stability under long term storage conditions at the following time points: 0, 1, 2, 3, 6, 9, 12, 24, 36, 48, 60, 72 and 84 months. The other three lots are being tested at the same time points as the lot 3-FIN-1512 under long term storage conditions, except for the 1 and 2 month time points.

Tests that are used to assess the quality attributes of the samples on stability are: appearance, pH, protein concentration, icIEF, non-reduced and reduced SDS-PAGE, SE-HPLC, PAA3, LNA bioassay, sterility and subvisible particulates (≥10 µm, ≥25 µm). Two additional tests: reduced and non-reduced CE-SDS methods are implemented in the stability program during the studies but the results are for information only and no specification has been set for this assay.

Summary of changes observed in four registration lots

Real time stability study (5°C±3 °C)

Cumulative 18 month real time stability data (5±3°C) from the three PV lots and cumulative 24 month real time stability data of DP lot 3-FIN-1512 and are provided with the BLA.

There is no obvious change observed in appearance except that visible particulates observed (see more information in later part in this section) under stability however they were within the DP release and stability specifications. (b) (4) All the available testing results met the stability acceptance criteria.

Reviewer's Comments: *The data support the DP are stable up to the last testing time points when stored at the recommended storage condition of 5° ± 3 °C.*

Stressed stability study (25°C/60% RH)

Cumulative 12 month accelerated stability data (25 ± 2°C/60%RH) from the three PV lots (one of the PV lot actually has data for T=18 time-point). Cumulative 24 months accelerated stability data on lot 3-FIN-1512 are provided with the BLA.

(b) (4)

Results of all other testing were basically unchanged and remain within the specification

Visible particulates

In the appearance testing, visible particulates have been observed intermittently in many of vials stored at 2-8°C or at 25°C/60% RH and were within the release and stability specifications for visible particulates. Table below shows visible particulates positive tests among all the current available test results (table is prepared by the reviewer using data reported in BLA section P.8.3)

Visible particulates are reported in obiltoxaximab samples on stability grogram

Lot	Storage Condition	Time point- Visible particulates observed	Time point- Free of visible particulates
3-FIN-1512	-20°C	(b) (4)	
	5°C		
	25°C/60%RH		

3-FIN-1702	5°C, upright	(b) (4)
	25°C/60%RH	
3-FIN-1703	5°C Upright	
	5°C Inverted	
	25C/60%RH Upright	
	25°C/60% RH Inverted	
3-FIN-1704	5°C Upright	
	5°C Inverted	
	25°C/60%RH Upright	
	25°C/60%RH Inverted	

All visible particulates observed in the 3-FIN-1512 lot were identified using FTIR as protein (b) (4). Particulates observed in the three PV lots are reported as protein (b) (4)

Elusys provides following information in its response to the Agency's information request (IR)-8 dated 2 Nov2015 regarding the identity of the (b) (4) material. According to the sponsor a (b) (4)

Reviewer's Comments: *The stability data of lot 3-FIN-1512 lot at -20°C storage for 24 months and stability data of lot 3-FIN-1703 and 3-FIN-1704 at invert position for 18 months are provided and the results are consistent with results summarized above.*

The data support the DP are stable up to the last tested time points when stored at the recommended storage condition of 5° ± 3°C. Based on the stability data provided it appears that the visible particulates (b) (4) *the sponsor was asked to set the expiry for obiltoxaximab drug product should be 18 months when stored at 5±3°C.*

Supportive Stability Study

Stability study that was conducted with obiltoxaximab DP lot PBR-0031-001, which was manufactured at (b) (4) using BDS manufactured by Baxter process. The study performed with obiltoxaximab DP stored at 5°C upright and horizontal and demonstrated that obiltoxaximab was stable for 60 months. The DP at the accelerated condition of 30°C/65%RH was stable for 6 months. The stability data of lot PBR-0031-001 are summarized below.

Real time storage condition (5°C)

Results of all the tests, including appearance, pH, A280, SDS-PAGE, PAA3, IEF, SE-HPLC, LNA, endotoxin, sterility at 60-month time point remained within the acceptable ranges and no obvious trend of change was shown.

Accelerated conditions

A 36 month accelerated study was performed at 30°C/65%RH storage condition. SE-HPLC fell to (b)(4)% monomer (specification (b)(4)%) at 9-month time point from (b)(4)% at T=0. At the end of the study T=36, the number of % monomer further reduced to (b)(4)%. The NR and reduced SDS-PAGEs were reported only matches profile of reference standard ((b)(4)% of RS). The potency by PAA3 and LNA remained within ranges at the end of the study. ***Reviewer's Comments***: *IEF reported only the pI of the main peak.*

A 6 month Stress study was performed at 40°C/65%RH. SE-HPLC fell to out of range at 3-month time point.

Proposed Expiry

Elusys proposes a DP expiry of 18 months at the recommended storage condition of 5°C ± 3°C. ***Reviewer's Comments***: *In response to FDA information request (IR)-11, dated 2 Nov. 2015. Elusys revised the proposed expiry from*(b)(4) *months to 18 months. The revised 18 months expiry is acceptable and supported by the current available stability data for 4 obiltoxaximab DP PV lots.*

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

(b)(4)

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

(b) (4)

3.2.A.3 Novel Excipients

No novel excipients are used in the manufacture of obiltoxaximab.

3.2.R Regional Information (U.S.A.)

3.2.R.1 Executed Batch Records

The effective obiltoxaximab DS commercial process master batch record (MBRs) and executed batch records of PV lot 342016 and post-PV lot 375105 (a post-PV improvement is introduced) are provided. The effective obiltoxaximab Drug Product commercial process MBR and EBRs of DP PV lot 3-FIN-1704 are provided.

Reviewer's Comments: *EBRs of one out the five DS PV runs and one out the three DP PV runs are provided.*

3.2.R.2 Method Validation Package

Reviewer's Comments: *The validation of analytical methods is provided in in section 3.2.S.4.2.*

3.2.R.3 Comparability Protocols

No comparability protocols are included in the BLA.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Information for the methods to detect antibodies to obiltoxaximab (ETI-204) in human serum is described in a study report ELR001 - Summary of Bioanalytical Methods Supporting ETI-204 Development (in 5.3.1.4.) The ADA testing for human serums is followed a tiered approach. The screening assay is an ECL based ELISA assay and performed by (b) (4) using validated protocol (b) (4) 157. The confirmatory assay includes an additional step, where free, exogenous ETI-204 is added to compete with the ruthenylated ETI-204 for binding to the antibody on the plate, resulting in a reduced signal. In this assay, affinity purified rabbit anti-ETI-204 are 1:1,000 and 1:10,000 dilution using normal human serum (NHS) and serves as the as low positive control (LPC) or high positive control (HPC) in the assay. The NHS are pool of normal human serum obtained from (b) (4) that also serves as negative control in this assay.

Screening Assay:

In brief, patient samples are first subjected to a minimum required dilution of 1:10. Then samples undergo a preparatory step with acidification to release anti-ETI-204 (ADA) from ETI-204 complexes. After acid dissociation, the released ADA bound to plates were incubated with biotinylated-ETI-204, allowing any anti-ETI-204 antibodies present in the sample to bind the labeled form of the drug. The biotinylated ETI-204/ADA complex is subsequently is added to streptavidin coated plates to immobilize the complex. The samples are re-acidified to free captured ADA. The solution containing the acidified ADA is added to a Meso Scale Discovery (MSD) plate and neutralized. Following an incubation period and wash, the coated ADA plate is incubated with ruthenylated-ETI-204. An ECL signal is generated when the ruthenium-coated ETI-204 detection reagent is exposed to carbon electrodes integrated into the microtiter plate. The ECL signals are acquired using a Sector Imager 2400 from Meso Scale Discovery. .

Validation of the Screening Assay to Detect anti-ETI-204 Antibodies in Human Serum

Reviewer's Comments: *The ECL method for the detection of anti-ETI-204 antibodies in human serum was initially validated in May 2009* (b) (4) *. An amendment 1 (and an addendum to this amendment) was made in August 2009* (b) (4) *. Two dilutions, 100 ng/mL and 1000 ng/mL of the purified anti-ETI-204 controls were tested and the assay precision and matrix selectivity were assessed. The results have met prior set acceptance and the new affinity purified rabbit anti-ETI-205 polyclonal antibodies in human serum is deemed suitable for use with the GCL-157 assay.*

In July 2014, an additional study was performed to qualify the (b) (4) *reagents and to extend the expiration date for control lot GCL-157-006. BLA describes the acceptance criteria of the validation study was* (b) (4) *."*

The minimum required dilution of 1:10 was established during method development.

Cut point: The cut point was determined by the analysis of sera from 51 normal healthy adults. Each serum sample was analyzed to generate one reportable result across six assay runs by two analysts in three days. These samples were analyzed with and without the addition of ETI-204. The distribution of ECL values varied significantly across assay runs. (b) (4) [redacted] In the amendment 1 (August 2009), a new statistical approach, a Box-Cox transformation, was applied and reported a cut point of 300 ECL units met the 5% false positive rate for this assay.

Reviewer's Comment: *The sample size for determining the assay cut point is acceptable. 5% false positive rate is acceptable. In response to FDA information request (IR)-8, dated 2 Nov 2015, Elusys reports that in clinical study AH104, AH109, AH110, total 46 samples were reported positive in the screening assay. Among them 37 samples were confirmed by tier 2 confirmatory assay, which gave a 20% false positive rate.* **Sensitivity**: Affinity purified anti-ETI-204 in the range from 0 to 2000 ng/ml in a pooled lot of serum. The background adjusted 300 units (cut point values) were interpolated against the rabbit anti-ETI-204 antibody calibration curve. The sensitivity of the assay was determined to be 27 ng/mL.

Reviewer's Comment: *The sensitivity of the assay is acceptable, which is higher than FDA recommendation, 250 - 500 ng/mL.*

Recovery / Selectivity: Accuracy was assessed indirectly by adding rabbit anti-ETI-204 Antiserum at low (1:10,000 dilution) and high (1:1,000) dilution) levels into 8 lots of normal human serum. The Mean % Recovery across all eight lots was 61.4% for the low antisera level and 65.0% for the high antisera level. All levels were greater than 50% when compared to buffer.

Precision: Rabbit anti-ETI-204 antiserum was diluted into a pooled lot of serum from normal healthy adults to prepare low (1:10,000 dilution), and high (1:1,000 dilution) positive controls. All controls were assayed to generate two reportable results per concentration across six assay runs by two analysts in three days. intra-assay precision (%CV) was 21.2% for the low control and 18.0% for the high control level; the inter-assay precision was 28.4% for the low control and 24.9% for the high control. The low QC inter-assay precision was 28.4%, which is just outside of the acceptance criteria stated in the Validation Plan 08-144. ***Reviewer's Comment***: *This variability is accounted for in the cut point assessment, which normalized variance over the range of response.*

Reviewer's Comment *A partial validation addendum (11-068, July, 2012) reports information for comparing and bridging the positive controls for previously used dilutions of raw antisera and affinity purified anti-ETI-204 (ng/mL) by analyzing specificity precision and using two sets of positive controls.*

Specificity: The specificity of an assay describes the ability of the assay to detect only the target analyte and can be affected by cross-reactivity and interference. Low (100 ng/mL) and high (1000 ng/mL) purified rabbit antiserum in matrix were analyzed in samples with the presence of 100 µg/mL of ETI-204. The average percent inhibition in binding response at all positive control was ≥ 95.0% and met acceptable specificity (≥ 50%). The non-related peptide specificity was not performed in the validation.

Interference from pharmacological concentrations of ETI-204: Potential of drug interference with the assay was also investigated by testing the effect of various concentrations of ETI-204 (0, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100 and 200 µg/mL) in serum samples containing purified anti-ETI-204 antibodies at concentration of 500 ng/mL or 1000 ng/mL. Increasing concentrations of ETI-204 resulted in increasing inhibition. 100 µg/mL ETI-204 in samples containing 500 ng/mL affinity purified rabbit anti-ETI-204 resulted in responses below the cut point (the new 300 ECL units).

Reviewer's Comment: *In Table 42 "ELISA Method to Detect Anti-ETI-204 Antibodies in Human serum" of Study report ELR001, it states that the assay can tolerate > 100 µg/mL of free ETI-204 in the sample before the signal drops below the cut point for a sample containing 500 ng/mL of Anti-ETI-204." However, in validation report 08-144 amendment 1, 100 µg/mL ETI-204 in samples containing 500 ng/mL affinity purified rabbit anti-ETI-204 resulted in responses 272 unit that is below the cut point (the new 300 ECL units).*

Reviewer's Comment: *PK curves demonstrates that ETI-204 serum concentration reduced to < 50 µg/mL approximately 5 - 6 weeks post IV. It suggests that the screening assay maybe used for samples collected after this period.*

Sample Stability: Short-term stability was assessed after storing the low (1:10,000) and high (1:1,000) anti-ETI-204 controls at room temperature and 2-8 °C for 4 and 24 hours. At both temperatures and durations, the % difference from reference for samples ranged from - 2.3% to 13.5%, within the acceptance criteria (within ± 25% of the reference sample) for all concentrations except the low concentration at RT for 24 hours that showed 26.9% difference from reference. The Sponsor concludes the samples are stable for at least 24 hrs at both 2-8°C and Rm. Freeze-Thaw Stability: Freeze/thaw stability was assessed following freeze/thaw cycles of the negative, low and high antiserum controls. Study data demonstrate the stability of anti-ETI-204 in human serum for at least eight freeze/thaw cycles (acceptance criteria is ± 25% of Reference Value).

Confirmatory Assay:

Samples evaluated during Screening (Tier 1) and with mean ECL responses above the assay cut point are tested for confirming the putative anti-drug antibody result. This assay use same assay procedure for the screening assay, except 100 µg/mL of ETI-204 is added with the Biotin-ETI-204 together for competing the binding with ADA. Anti-ETI-204 positive samples will tend, as expected, to exhibit a high calculated percent inhibition. Any sample showed ≥50% inhibition will be consider as ADA confirmed samples, and will be submitted to determine antibody titer

Reviewer's Comment: *The ≥50% inhibition positive criterion is acceptable the sponsor has shown a dose dependent inhibition of the signal in both high and low positive control when ETI-204 is added from 0-200 µg/mL range. The human samples tested positive by screening assay were all confirmed to be positive ADA by this assay. (Elusys response to FDA information request (IR)-8 dated 2 Nob 2015).*

Neutralizing ADA Detection Assay

During the development of obiltoxaximab, a neutralizing anti-drug antibody (Nab) detection assay was developed. This is a cell-based bioassay that utilized the macrophage cell line RAW 264.7, Lethal toxin and obiltoxaximab as the assay system; and cell viability as the end point to detect neutralizing antibodies to obiltoxaximab in human serum samples. The method procedures

are, in brief, as follows: The RAW 264.7 cells are plated into a 96-well plate, the control and serum samples are performed hydrolysis / neutralization treatments to release possible immune complexes, and then incubated with obiltoxaximab. The samples and controls are subsequently, together with LeTx, added to the cells. At the end of incubation, an MTT assay is employed to assess the cell viability.

The assay was initially validated in April, 2013 (study 8262-947) and an amendment was made to it in Oct. 2012. During the studies in the development of obiltoxaximab, this Nab detection assay was used to test patient samples. However, it was found that this method was failed to generate useful data because of the drug interference. The obiltoxaximab concentrations in patient serums collected 72 days post administration are about 10 µg/mL, which is significantly above the drug tolerance of the assay (500 ng/mL for low positive control level). This BLA does not discuss the application of this assay in studies but contains the initial validation reports of this assay in submission.

Reviewer's Comment: *NAb assay is not suitable for detecting neutralizing antibody as it is sensitive to the levels of drug that is present in the patients' immunogenicity samples.*

Reviewer's Comments: *To detect anti-drug antibody (ADA) a tiered approach ECL-based binding antibody assay is used that include initial screening assay followed by confirmatory assay and titration of the samples that were found confirmed positive. The sensitivity of the screening assay was determined to be 27ng/mL. A sample containing 500 ng/mL surrogate ADA is shown to detect antibodies to drug in the presence of obiltoxaximab levels of up to 50µg/mL. This response is generally considered clinically meaningful. Overall, the ADA screening assay is considered to be suitable for the intended use. The sponsor also developed a cell-based assay to detect neutralizing antibody (NAb assay) response to obiltoxaximab. However, this assay was found to be very sensitive to the presence of drug in the patients' samples. The tolerance of the NAb assay for obiltoxaximab was shown to be approximately 1000 ng/mL and 500ng/mL for high ADA and low ADA positive controls. These levels are below obiltoxaximab serum concentration that is expected to be present in the patients' immunogenicity samples. Therefore this assay is not considered suitable for the intended use. After consulting with the clinical pharmacology discipline reviewer it was determined that it is acceptable because a) this product is given as a single dose; b) the ADA response is only detected in 3% of clinical study population; and c) the presence of ADA do not appear to have any discernable effect on obiltoxaximab PK following IV administration. Based on this risk assessment and evaluation it was concluded that the risk of developing the neutralizing antibody are minimal for this product.*