

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761073Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761073
Office of Product Quality Application Team Lead Review
Review Number: Second Round
Review Date: June 1, 2019

Drug Name/Dosage Form	Kanjinti (trastuzumab-anns)/ for injection
Strength/Potency	420 mg/vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indications	Treatment of HER2 overexpressing breast cancer Treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Applicant/Sponsor	Amgen, Inc.

Product Overview

Kanjinti (trastuzumab-anns) is a proposed biosimilar to US-licensed Herceptin. Kanjinti is a humanized IgG1κ monoclonal antibody that binds human epidermal growth factor receptor 2 (HER2). A proposed mechanism of action is inhibition of ligand-independent HER2 signaling, which in turn inhibits the proliferation of tumor cells that overexpress HER2. A second proposed mechanism of action is antibody-dependent cellular cytotoxicity (ADCC) mediated through concomitant binding to HER2 and Fcγ receptors on the surface of immune system effector cells, which leads to anti-tumor immune responses. The drug substance is produced by recombinant DNA technology in cultures of Chinese Hamster Ovary cells. The final drug product is supplied in vials as a white to pale yellow lyophilized powder for reconstitution with bacteriostatic water for injection (bWFI) or sterile water for injection (sWFI). Kanjinti drug product is formulated in 4.2 mM L-histidine, 51 mM α,α-trehalose, 0.008% (w/v) polysorbate 20 at pH 6 (b) (4). The formulation (b) (4) the same as US-licensed Herceptin (trastuzumab) (hereinafter referred to as US-Herceptin).

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Lei Zhang	OPQ/OBP/DBRRII
Analytical Similarity	Lei Zhang	OPQ/OBP/DBRRII
Drug Product	Lei Zhang	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facilities	Wayne Seifert	OPQ/OPF/DIA
Facilities Team Lead	Zhihao Peter Qiu	OPQ/OPF/DIA
Microbiology Drug Substance	Maxwell Van Tassell	OPQ/OPF/DMA
Microbiology Drug Product	Jessica Hankins	OPQ/OPF/DMA
Microbiology QAL	Reyes Candau-Chacon	OPQ/OPF/DMA
Application Technical Lead	Patrick Lynch	OPQ/OBP/DBRRII

Tertiary Reviewer for OBP	Emily Jing	OPQ/OBP/DBRRII
RBPM	Andrew Shiber	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Charlene Wheeler	OND/OHOP/DOP1
Cross-disciplinary Team Lead	Jenny Gao	OND/OHOP/DOP1
Medical Officer	Danielle Krol	OND/OHOP/DOP1
Pharm/Tox	Kimberly Ringgold/Tiffany Ricks (TL)	OND/OHOP/DHOT
Clinical Pharmacology	Salaheldin Hamed/Pengfei Song (TL)	OTS/OCP/DCPV
CMC Statistics	Yu-Yi Hsu/ Meiyu Shen (TL)	OTS/OB/DBVI

1. Names:

- a. Proprietary Name: Kanjinti
- b. Trade Name: Kanjinti
- c. Non-Proprietary: Trastuzumab-anns

Submissions Reviewed:

Submission(s) Reviewed (OPQ office)	Document Date
STN 761073/38 (OBP, OPF)	December 28, 2018
STN 761073/39 (OPF)	January 22, 2019
STN 761073/40 (OPF)	January 23, 2019
STN 761073/42 (OBP)	March 8, 2019
STN 761073/43 (OBP)	April 15, 2019
STN 761073/44 (OPF)	April 17, 2019
STN 761073/45 (OBP)	April 23, 2019
STN 761073/46 (OPF)	May 3, 2019
STN 761073/47 (OBP)	May 10, 2019
STN 761073/48 (OBP, OPF)	May 20, 2019

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

Refer to the Integrated Quality Review (Referred to as Executive Summary or Application Team Lead Review) dated May 22, 2018 for an assessment of Drug Master Files (DMF) and supporting documents referenced in the original BLA.

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761073 for Kanjinti manufactured by Amgen, Inc. This memo documents the review of the Amgen's response to deficiencies communicated in a Complete Response (CR) Letter issued on May 25, 2018, pertaining to cGMP observations identified on inspection of the proposed drug product manufacturing facility, (b) (4). The applicant adequately addressed these deficiencies and additional comments communicated in the May 25, 2018 CR Letter. The data submitted in this application are adequate to support the conclusion that the manufacture of Kanjinti is well-controlled and leads to a product that is pure and potent. The analytical similarity data submitted in the application demonstrate that Kanjinti is highly similar to US-Herceptin. A sufficient analytical component of the three-way scientific bridge was established to support the use of EU-approved Herceptin (EU-Herceptin) as a comparator in clinical trials supporting this application. Therefore, OPQ recommends that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance:
 - Immunex Rhode Island Corporation (referred to as Amgen Rhode Island or ARI)
40 Technology Way
West Greenwich, RI 02817

(b) (4)

- Drug Product:
 - Amgen Technology (Ireland) Unlimited Company (referred to as ADL)
Pottery Road
Dun Laoghaire, Co. Dublin, Ireland

- Fill size and dosage form: 420 mg/vial for injection, multi-dose vial

- Dating period:

- Drug Product: 36 months; 2-8°C
- Drug Substance: (b) (4) months; (b) (4)
- Not packaged
- Stability Option:

- We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Exempt specified according to 21 CFR 601.2(a).

C. Benefit/Risk Considerations:

Refer to the Executive Summary memo dated May 22, 2018 for Benefit/Risk Considerations assessed during the first review cycle.

In response to the CR Letter dated May 25, 2018, Amgen updated the manufacturer information with new facilities for the manufacture of drug substance and drug product. ADL is added as a new drug product facility and ARI is added as an alternate drug substance manufacturing facility. Analytical data and information provided in the resubmission support the conclusion that there are no meaningful differences between drug substance or drug product lots produced at the new facilities compared to those produced at facilities in the initial application. The manufacturing processes for Kanjinti drug substance are well controlled and consistently produce product that is pure and potent. The drug substance processes are qualified for removal of impurities and inactivation or removal of adventitious agents.

The overall control strategy for drug substance and drug product is comprehensive for control of raw materials, process performance, and product quality attributes. ADCC activity of Kanjinti is controlled (b) (4)

At the Agency's request, which was communicated as additional comments in the May 25, 2018 CR Letter, Amgen agreed to implement an FcγRIIIa binding test to the drug substance release specification and to conduct additional characterization to further understand the impact of drug product manufacturing and stability conditions on Fc functions. This information provides additional assurance that ADCC activity is fully controlled in commercial Kanjinti lots for the lifecycle of the product. The current proposed manufacturing control strategy is sufficient to ensure process consistency and product quality.

The commercial manufacture of Kanjinti drug substance a (b) (4) and ARI, and drug product at ADL is recommended for approval by OPQ. Additional data and information to support the overall quality assessment are in the OPQ primary technical reviews for product quality, microbiology, facilities, and labeling. OPQ primary technical reviews are located in Panorama.

II. Summary of Quality Assessments:

A. Analytical Data Assessment

Regarding the analytical similarity assessment, there are no changes to the conclusions reached in the first review cycle. Refer to the Executive Summary memo dated May 22, 2018 for a detailed assessment of analytical similarity data.

Amgen updated the analytical similarity assessment in the resubmission to include results from 5 additional lots of Kanjinti drug substance produced at ARI, and 3 additional lots of drug product produced at ADL. The updated analytical characterization data are comprehensive for structural and biological product quality attributes. Analytical results from additional lots of Kanjinti are consistent with those evaluated during the first review cycle. The updated analytical similarity assessment confirms the previous conclusion made during the first review cycle that Kanjinti is highly similar to US-Herceptin. Additional information is in the Product Quality primary technical review.

B. CQA Identification, Risk and Lifecycle Knowledge Management

This section from the May 22, 2018 Executive Summary memo is updated to reflect additional control strategy information provided in the resubmission. Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance and drug product.

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

CQA	Risk	Origin	Control Strategy	Other
Inhibition of Proliferation (potency)	Efficacy	Intrinsic to the molecule. Impacted by isomerization (HC Asp¹⁰²), aggregation, fragments, and deamidation. Decreases upon exposure to heat and light. Minimal change is expected when stored under recommended storage conditions.	(b) (4)	Cell based bioassay method is stability indicating.
HER2 binding (potency)	Efficacy	Intrinsic to the molecule. Impacted by fragments. Decreases upon exposure to heat.		N/A

		Minimal change is expected when stored under recommended storage conditions.		
Effector function/ADCC (potency)	Efficacy	Intrinsic to the molecule. Impacted by levels of core fucose and galactosylation. Decrease upon exposure to heat consistent with decrease in HER2 binding. Minimal change is expected when stored under recommended storage conditions.	(b) (4)	No CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A
Isomerization at Asp ¹⁰² in the HC CDR (product-related impurity)	Efficacy (isomerization may reduce potency or effector function) and Immunogenicity	Production culture. May increase during storage of DP. Increases upon exposure to heat and low pH.		CEX-HPLC method is stability indicating.
Dimer/High Molecular Weight (HMW) Species/Aggregates (Product-related impurities)	Efficacy and Immunogenicity	Production culture and potential minor impact from DP process. May increase during storage of DP. Increase upon exposure to heat and light.		SE-UHPLC method is stability-indicating.
Fragments (Product-related impurity)	Immunogenicity and Efficacy	Cell culture process Increase upon exposure to heat. No change through expiry when stored		N/A

		under recommended conditions.		
Glycosylation— afucosylation (Product related variant)	Efficacy (Effector function)	Cell culture process	(b) (4)	N/A
Glycosylation— high mannose (Product related variant)	Efficacy (Effector function) and Pharmacokinetics	Cell culture process		N/A
Glycosylation— galactosylation (Product related variant)	Efficacy (Effector function)	Cell culture process		N/A
Partially reduced species (Product-related impurity)	Efficacy	Production culture and harvest processes Increases upon exposure to heat. Minimal change is expected under recommended storage conditions.		N/A
Deamidation at Asn30 Asn55 (Product-related impurities)	Efficacy and Immunogenicity	Manufacturing process Increases upon exposure to heat. Minimal change is expected under recommended storage conditions.		CEX-HPLC method is stability-indicating.
Sequence variants at T259A and N84T (Product-related variants)	Immunogenicity	Production cell line		N/A
pH (General)	Safety and Efficacy	Formulation		N/A

Protein concentration (General)	Efficacy	Manufacturing process	(b) (4)	N/A
Osmolality (General)	Safety	Formulation		N/A
Polysorbate concentration (General)	Safety	Formulation		N/A

C. Drug Substance trastuzumab-anns Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

This section from the May 22, 2018 Executive Summary memo is updated to include additional manufacturing process and control strategy information provided in the resubmission. Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (general)	Safety	Manufacturing process	(b) (4)	N/A
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (process-related impurity)	Low hypothetical safety or immunogenicity risk	Production cell line		N/A

Protein A (process-related impurity)	Immunogenicity	Leaching of protein A (b) (4)	(b) (4)	N/A
(b) (4)	Safety	Process-related impurity used (b) (4)		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used (b) (4)		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				

			(b) (4)	
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
Viruses (Contaminant)	Safety	Contamination during manufacture		N/A
Mycoplasma (Contaminant)	Safety	Contamination during cell culture operations		N/A
Leachables (Process-related impurity)	Safety	Manufacturing components and DS container closure system (CCS)		N/A
Bacterial endotoxins (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process		N/A

Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	(b) (4)	N/A
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- **Description:**

Trastuzumab-anns is a recombinant humanized IgG1κ monoclonal antibody produced in CHO cells that targets human epidermal growth factor receptor 2 (HER2). The antibody consists of two heavy chains (449 amino acids each) and two light chains (214 amino acids each). Each heavy chain contains an N-linked glycan site at asparagine 300 (Asn300) with greater than 99.8% occupancy. The predominant glycan species are asialylated core fucosylated biantennary with varying degrees of terminal galactose. Trastuzumab-anns has an average molecular weight of 148,222 Da and an isoelectric point of 8.8 (main species). The theoretical and experimental extinction coefficient is 1.5 cm⁻¹ (mg/mL)⁻¹ at A₂₈₀ nm.

- **Mechanism of Action (MoA):**

Multiple mechanisms of action are proposed for trastuzumab-anns, which binds to the extracellular domain subdomain IV of HER2. Overexpression of HER2 on cancer cells results in persistent and ligand-independent activation of downstream signaling, which in turn leads to aberrant cell proliferation. Trastuzumab-anns binding to HER2 blocks this ligand-independent signaling in cancer cells, thereby inhibiting cellular proliferation. A second proposed mechanism of action is activation of antibody-dependent cellular cytotoxicity (ADCC) through concomitant binding of trastuzumab-anns to HER2 on cancer cells and Fcγ receptors on immune effector cells. Trastuzumab-anns also binds to complement component 1q (C1q) of the classical complement pathway. However, complement-dependent cytotoxicity (CDC) is not detected for trastuzumab-anns and therefore not considered a major mechanism of action.

- **Potency Assay:**

Inhibition of proliferation is tested by a quantitative cell-based assay using BT-474 human breast tumor cells that overexpress HER2. Cell proliferation is measured using a luminescent assay reagent that detects ATP. The measured luminescent signal is proportional to the amount of ATP, which is proportional to the number of cells present. Trastuzumab-anns inhibits BT-474 cell proliferation resulting in a dose-dependent loss of luminescent signal. Relative potency values are calculated using model curve fits from four-parameter logistic curves of dose response data. Potency is reported as a percentage relative to the reference standard. The cell-based bioassay is appropriately validated.

Asparagine-linked (N-linked) oligosaccharides are assessed by hydrophilic interaction chromatography (HILIC) glycan mapping as surrogate for ADCC activity. The N-linked glycan are enzymatically released using N-glycosidase F (PNGase F) and the terminal N-acetylglucosamine (GlcNAc) is derivatized with a fluorophore. The labeled glycan are

then separated using a hydrophilic interaction column and evaluated by a fluorescence detector. (b) (4)

. Additional information is located in the Product Quality technical reviews.

- **Reference Materials:**

A two-tier reference standard qualification program is in place consistent with ICH Q6B recommendations. The current primary and working reference standards are stored at -

(b) (4)

- **Critical starting materials or intermediates:**

A two-tiered cell banking system consisting of a master cell bank (MCB) and working cell bank (WCB) is in place to ensure continued source of product. The production cell

(b) (4)

- **Manufacturing process summary:**

The DS manufacturing process at (b) (4) starts with (b) (4)

(b) (4)



The BLA contains sufficient information and validation results that indicate the raw material program, facilities and equipment, manufacturing process, release, and stability programs are adequately controlled resulting in the production of a consistent product. Additional information is in the Product Quality and DS Microbiology primary technical reviews.

- **Container closure:**

(b) (4)



- **Dating period and storage conditions:**

The data provided in the BLA support the establishment of a shelf life of (b) (4) months for trastuzumab-anns drug substance when stored at (b) (4)

D. Drug Product [Kanjinti] Quality Summary:

This section from the May 22, 2018 Executive Summary memo is updated to reflect current manufacturing process and control strategy information provided in the resubmission. 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.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout DP manufacturing process	(b) (4)	N/A
Endotoxin (Contaminant)	Safety (immunogenicity) and purity	Endotoxin can be introduced through raw materials, throughout the manufacturing process.		N/A
Container Closure Integrity (Contaminant)	Loss of sterility during the product shelf-life	Container closure breaches during manufacturing or storage		N/A
Color and clarity of solution (General)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Appearance of reconstituted solution—visible particles (product or process-related impurities)	Safety and Immunogenicity	Manufacturing process, formulation, interaction with container closure system		N/A
Appearance—lyophilized cake	Safety and Efficacy	Manufacturing process		N/A
Moisture content	Safety and Efficacy	Manufacturing process		N/A

Reconstitution time	Safety and Efficacy	Manufacturing process, formulation	(b) (4)	N/A
Subvisible particles	Safety and Immunogenicity	Manufacturing process and storage		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		N/A

- **Potency and Strength:**

Kanjinti is supplied at 420 mg/vial. Potency is defined as the percent activity relative to reference material. The cell-based potency assay is the same as described in the DS section of this memo. The DP specification for potency is (b) (4)% for release and stability.

- **Summary of Product Design:**

Kanjinti is supplied in a 50 mL glass vial as a sterile, multi-dose, preservative-free lyophilized powder for reconstitution. The reconstituted product is intended for dilution in saline for IV infusion. Kanjinti is formulated in 4.2 mM L-histidine, 51 mM α,α -trehalose, 0.008% (w/v) polysorbate 20 at pH 6 (b) (4). Reconstitution with 20 mL diluent yields a solution containing 21 mg/mL trastuzumab-anns at a pH of 6 (b) (4). The deliverable amount is 420 mg. Kanjinti is intended for reconstitution with 20 mL bacteriostatic WFI (bWFI), with 0.9% to 1.1% benzyl alcohol as a preservative for multi-dose, or 20 mL of sterile WFI (sWFI) for single use. When reconstituted with bWFI, Kanjinti is stored for up to 28 days at 2-8°C.

- **List of Excipients:**

Excipients include L-Histidine (USP, PhEur, JP), L-Histidine hydrochloride monohydrate (PhEur, JP), α,α -trehalose dihydrate (USP/NF, PhEur, JP), and polysorbate 20 (USP/NF, PhEur, JPE).

- **Reference Materials:**

The same reference material is used for testing DS and DP.

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**

The primary container closure system for Kanjinti consists of a 50 mL (b) (4) glass vial that is closed with a 20 mm (b) (4) stopper and sealed with a 20 mm flip-off aluminum seal with plastic button. The secondary packaging consists of a carton constructed of solid paperboard to shield the product from light.

- **Dating period and storage conditions:**

The stability data in the BLA support a shelf life for Kanjinti of 36 months when stored at the recommended storage condition of 2-8°C. Stability data in the BLA support storage of the reconstituted product for 28 days at 2-8°C protected from light.

E. Novel Approaches/Precedents:

None

F. Any Special Product Quality Labeling Recommendations:

Store Kanjinti refrigerated at 2-8°C and protected from light. Do not shake. Do not freeze the reconstituted solution.

G. Establishment

In response to the CR Letter deficiency, Amgen provided updated facilities information. The below Overall Facility Recommendation table reflects the updated establishment information for manufacture and testing of drug substance and drug product.

Overall Facility Recommendation:				
Drug Substance				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
(b) (4)			Drug substance manufacture	Acceptable
			Drug substance in-process and lot release testing	
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320	2026154	Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank storage Manufacture of working cell banks	Acceptable

Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road Dun Laoghaire, Co. Dublin, Ireland	3002808497	Drug substance in-process, lot release and stability testing, and storage	Acceptable
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817	3003359885	Drug substance manufacture Drug substance in-process, lot release and stability testing Unprocessed bulk mycoplasma testing Working cell bank storage	Acceptable
(b) (4)			Unprocessed bulk mycoplasma and adventitious virus testing	Acceptable
			Unprocessed bulk mycoplasma and adventitious virus testing	Acceptable
			Unprocessed bulk mycoplasma and adventitious viral testing	Acceptable

Drug Product				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320	2026154	Drug product lot release and stability testing.	Acceptable
Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road Dun Laoghaire, Co. Dublin, Ireland	3002808497	Drug product manufacture Packaging and labeling	Acceptable

			Drug product lot release and stability testing.	
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817	3003359885	Drug product lot release and stability testing	Acceptable

H. Facilities:

During the resubmission review cycle, a pre-licensure inspection (PLI) was conducted from April 15, 2019 through April 19, 2019 at the Amgen Rhode Island drug substance manufacturing facility. The PLI included assessment of the following systems: Quality, Facility and Equipment, Product, Materials, and Laboratory. Analytical similarity data generated at the site was also assessed. A four-item Form FDA 483 was issued to the Firm covering deficiencies pertaining to procedures for investigating out-of-specification results, oversight for instrument calibration and maintenance, investigation of deviations, and oversight for critical manufacturing steps. The CDER inspectors recommended VAI. The firm's response to the objectionable conditions was considered adequate by CDER/OPQ/OPF/DIA with a final classification of VAI under CMS Work Assignment #275275.

Refer to the Executive Summary memo dated May 22, 2018 for facilities information assessed during the first review cycle. Additional information is located in the primary technical review for facilities.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. Annual stability protocol for drug substance
2. Stability protocol for extension of drug substance shelf life
3. Protocol for qualification of future working cell banks
4. Protocol for qualification of future primary and working reference standards

(b) (4)

ii. Outstanding issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

1. Annual stability protocol for drug product
2. Stability protocol for extension of drug product shelf life
3. Stability protocol (b) (4)
4. Comparability protocol for addition of Production Module 2 at Amgen Technology Ireland UC, Dun Laoghaire, Ireland as an alternate manufacturing facility for drug product.

ii. Outstanding issues/residual risk: 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 source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity		X	
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)	X		
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]		X	
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	X	
23.		Process	X	
24.		Analytical Methods	X	
25.		Other	X	
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)	X		
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients	X	
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin	X	
35.		Novel	X	
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release			
40.	Other {fill-in}		X	



Patrick
Lynch

Digitally signed by Patrick Lynch

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BLA 761073

KANJINTI (trastuzumab-anns)

Amgen, Inc.

OBP CMC Review Data Sheet

1. BLA#: 761073/0037

2. Review Date: May 9, 2019

3. Primary Review Team:

- a. Medical Officer: Danielle Krol
Jennifer Gao (CDTL)
- b. Pharm/Tox: Kimberly Ringgold
Tiffany Ricks (TL)
- c. Product Quality Team: Lei Zhang (DS, DP, Analytical Similarity)
Patrick Lynch (TL, ATL)
Emily Jing (Review Chief)
Maxwell Van Tassell (Microbiology DS)
Jessica Hankins (Microbiology DP)
Reyes Candau-Chacon (Microbiology QAL)
- d. Facilities: Wayne Seifert
Zhihao Qiu (TL)
- e. Clinical Pharmacology: Salaheldin Hamed
Pengfei Song (TL)
- f. Statistics: Yu-Yi Hsu (CMC Stats Reviewer)
Meiyu Shen (CMC Stats TL)
- g. OBP Labeling: Vicky Borders-Hemphill
- h. RBPM: Andrew Shiber
- i. RPM: Charlene Wheeler

4. Major GRMP Deadlines:

- a. Re-submission planning meeting: January 30, 2019
- b. Mid-cycle meeting: March 20, 2019
- c. Primary review due: May 29, 2019
- d. Secondary review due: June 3, 2019
- e. BSUFA action date: June 28, 2019

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #1	April 17, 2019
Information Request #2	May 17, 2019

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761073/0045 (Response to IR #1)	April 23, 2019	Yes
761073/0048 (Response to IR #2)	May 20, 2019	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Kanjinti
- b. Trade Name: Kanjinti
- c. Non-Proprietary Name/USAN: Trastuzumab-anns
- d. CAS Name: 1446410-98-5
- e. Common Name: ABP 980
- f. INN Name: Trastuzumab
- g. Compndial Name: Not Applicable
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P04626
(ERBB2_HUMAN) [ABP 980]
- i. Other names: Not Applicable

8. Pharmacological Category: Therapeutic recombinant humanized monoclonal IgG1 antibody to HER2

9. Dosage Form: For injection

10. Strength/Potency:

- (i): The concentration/strength of the Drug Product: 420 mg
- (ii): Type of potency assay(s): Cell based proliferation inhibition bioassay

11. Route of Administration: Intravenous (IV) infusion

12. Referenced Drug Master Files (DMF): Refer to primary technical review for the first review cycle, dated May 23, 2018.

13. Inspectional Activities:

A pre-licensure inspection (PLI) was conducted from April 15, 2019 through April 19, 2019 at the following facility:

Immunex Rhode Island Corporation
40 Technology Way, West Greenwich, Rhode Island 02817, US
FEI 3003359885

The PLI covered the manufacturing operations for ABP 980 DS under BLA 761073 and (b) (4). The PLI was conducted by reviewers from OBP (William Hallett, Yetao Jin, Lei Zhang) and OPF/DIA (Ziyang Su, Zhihao Peter Qiu). The PLI covered quality assessment procedures, manufacturing process, facilities and equipment, material management, data entry, contamination prevention, laboratory control, and training programs. Assessment was made in accordance with ICH Q7A. A four items 483 was issued with respect to deviation procedures, quality unit oversight over instrumentation calibration and maintenance, deviation investigation, and quality unit oversight over critical manufacturing steps.

14. Consults Requested by OBP: None

15. Quality by Design Elements:

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

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

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation:

The data submitted in BLA 761073 support the conclusion that the manufacturing process of Kanjinti (trastuzumab-anns) is well controlled and leads to a product that is pure and potent. With respect to analytical similarity, data provided in the submission support that Kanjinti is highly similar to US-licensed Herceptin. From the product quality perspective, I recommend Kanjinti (trastuzumab-anns) be approved for human use under conditions specified in the package insert.

II. List of Deficiencies to be Communicated: NA

III. List of Post-Marketing Commitments/Requirements: None

IV. Review of Common Technical Document - Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c). This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This waiver is appropriate and found acceptable.

V. Primary Container Labeling Review

The primary and secondary container closure labeling review is performed in a separate review by Vicky Borders-Hemphill.

VI. Review of Common Technical Document- Quality Module 3.2: Refer to the review memo

VII. Review of Immunogenicity Assays - Refer to the primary technical review from the first review cycle, dated May 23, 2018.

Resubmission Overview

This BLA was initially submitted on July 28, 2017. The Agency issued a Complete Response Letter (CRL) on May 25, 2018 to the Sponsor after review of the original submission. This resubmission (SN#0037) was received on December 28, 2018. The reason for the Complete Response action during the first review cycle is described as below:

Facility Inspections: During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

This memo documents the review of Amgen's response to deficiencies communicated in a Complete Response (CR) Letter issued on May 25, 2018, pertaining to cGMP observations identified on inspection of the proposed drug product manufacturing facility.

In the initial BLA, (b) (4) was the proposed drug substance manufacturing facility and (b) (4) was the proposed drug product (b) (4) manufacturing facility. In the initial BLA, the Applicant sought approval for the 420 mg multi-dose vial presentation, (b) (4). In this BLA resubmission, the Applicant is replacing (b) (4) with Amgen Technology Ireland UC (ADL) as the proposed drug product manufacturer. With the withdrawal of (b) (4), the Applicant is also proposing (b) (4) the multi-dose label claim for the 420 mg presentation. Furthermore, the Applicant is adding Immunex Rhode Island Corporation (also referred to as Amgen Rhode Island, or ARI) as an alternate drug substance manufacturing site for ABP 980 to support the drug product manufacturing process validation at ADL. With introduction of ARI and ADL manufacturing sites, the analytical similarity assessment is updated with ARI and ADL ABP 980 lots. This review will only discuss the new drug substance and drug product manufacturing facilities, ARI and ADL, and any changes or updates to information provided during the initial review cycle. Information that has been discussed during the initial review cycle won't be repeated here, unless necessary to facilitate the review.

Review

S. Drug Substance

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The facilities for ABP 980 manufacture and testing are updated and listed in Table 1. The updated contract testing laboratories are listed in Table 2. The release and stability tests executed at each DS facility are listed in Table 3.

Table 1. Drug Substance Facility Responsibilities

Facility	Address	Responsibility	FDA Registration Number
(b) (4)		Drug substance manufacture Drug substance in-process and lot release testing	(b) (4)
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320 USA	Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank storage Manufacture of working cell banks	FEI: 2026154 DUNS: 039976196
Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road, Dun Laoghaire, Co. Dublin, Ireland	Drug substance in-process, lot release and stability testing, and storage	FEI: 3002808497 DUNS: 896293920
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817 United States	Drug substance manufacture Unprocessed bulk mycoplasma testing Drug substance in-process, lot release and stability testing Working cell bank storage	FEI: 3003359885 DUNS: 968084785

FEI= Facility Establishment Identifier
DUNS = Data Universal Numbering System

Table 2. Contract Testing Laboratories

Facility	Address	Type of Testing	FDA Registration Number
(b) (4)		Unprocessed bulk mycoplasma and adventitious viral testing	(b) (4)
		Unprocessed bulk mycoplasma and adventitious viral testing	
		Unprocessed bulk mycoplasma and adventitious viral testing	

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

Table 3. Sites Used for ABP 980 Drug Substance Release/Stability Testing

Test	(b) (4)	Testing Site		
		ATO	ARI	ADL
Appearance	-	X	X	X
ABP 980 ELISA	-	X	X	X
CEX-HPLC	-	X	X	X
SE-UHPLC	-	X	X	X
Bacterial endotoxins	X	-	X	-
Bioburden	X	-	X	-
Proliferation inhibition bioassay	-	X	X	X
Protein concentration	X	X	X	X
pH	X	X	X	X
Polysorbate 20	-	X	X	X
Glycan map	-	X	X	-

ATO = Amgen Thousand Oaks; ADL = Amgen Technology Ireland, ARI = Amgen Rhode Island
"X" in each cell indicates that the site has been qualified to perform this testing

Reviewer Comment: Compared with information submitted during the first review cycle, the following are changes regarding the facilities' responsibilities: 1) ARI's responsibility is extended to include DS manufacture and working cell bank storage (Table 1); 2) the release/stability tests executed at ARI are extended to include ABP 980 ELISA, bacterial endotoxins, bioburden, proliferation inhibition bioassay, protein concentration, pH, and glycan map (Table 3); 3) (b) (4) is removed as a backup in-process, lot release and stability testing facility for ABP 980 DS (IR response dated May 20, 2019); 4) (b) (4) is added as a new contract testing laboratory for unprocessed bulk mycoplasma and adventitious viral testing (Table 2). These changes are marked as yellow by the reviewer in Table 1 to 3 above.

**3.2.S.2.2 Description of Manufacturing Process and Process Controls &
3.2.S.2.4 Controls of Critical Steps and Intermediates**

(b) (4)

P: Drug Product

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

The ABP 980 drug product (DP) is supplied in a glass vial as a sterile, white to pale yellow, preservative free lyophilized powder for reconstitution. The container closure system for the ABP 980 DP consists of a 50 cc (b) (4) glass vial, (b) (4) stopper, and aluminum seal with flip-off button. The 420 mg presentation is intended for reconstitution with 20 mL of bacteriostatic water for injection (bWFI) containing 0.9% to 1.1% benzyl alcohol for multi-dose injection, or with 20 mL of sterile water for injection (sWFI) for single use for patients with known hypersensitivity to benzyl alcohol. Reconstitution with the appropriate quantity of diluent (bWFI or sWFI) yields a solution containing 21 mg/mL of ABP 980 at a pH of approximately 6 (b) (4). The reconstituted product is a colorless to slightly yellow liquid. The quantitative and qualitative composition of ABP 980 DP is listed as in Table 1.

Table 1. Quantitative and Qualitative Composition of ABP 980 Drug Product

Component	Grade	Function	Recoverable Content (420 mg Vial)	Concentration ^a
ABP 980	In house ^b	Active ingredient	420 mg	21 mg/mL
L-Histidine	USP, PhEur, JP	(b) (4)	6.1 mg	0.30 mg/mL
L-Histidine hydrochloride monohydrate	PhEur, JP		9.5 mg	0.47 mg/mL
α,α-Trehalose dihydrate	USP/NF, PhEur, JP		382 mg	19 mg/mL
Polysorbate 20	USP/NF, PhEur, JPE		1.7 mg	0.08 mg/mL

^a Target concentration upon reconstitution.

^b Tested to internal specifications (3.2.S.4.1, Specification).

3.2.P.2 Pharmaceutical Development

3.2.P.2.3 Manufacturing Process Development

(b) (4)

3.2.R Regional Information

Updated Analytical Similarity Assessment

Lots included in the Updated Analytical Similarity Assessment

The following ABP 980 drug product (DP) lots (Table 1 and Table 2) and drug substance (DS) lots (Table 3) were included in the updated analytical similarity assessment. DP process validation lots manufactured at Amgen Technology Ireland Unlimited Company (ADL) and DS process validation lots manufactured at Amgen Rhode Island (ARI) were included (marked as yellow). The ADL DP lots added were all in 420 mg presentation. All ABP 980 lots previously included in the analytical similarity assessment during the original review cycle remained unchanged in this update.

Table 1. ABP 980 Lots Included in the Analytical Similarity Assessment (150 mg Presentation)

Drug Product Lot Number	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Drug Product Intended Use ^a	Drug Substance Lot Number ^b	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
130028	(b) (4)	Dec 2013	Clinical, nonclinical	0010200648	(b) (4)	Nov 2013	Clinical, nonclinical, stability
130029		Jan 2014	Development	0010195050		Dec 2013	Clinical, stability
130030		Mar 2014	Clinical	0010195050 1401-085		Dec 2013 Feb 2014	Clinical, stability Clinical
0010198170	ATO	Apr 2014	Clinical, stability	0010195050		Dec 2013	Clinical, stability
0010204750	ATO	May 2014	Clinical	0010195050		Dec 2013	Clinical, stability
0010203282	ATO	Aug 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010203432	ATO	Sep 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010203498	ATO	Oct 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010208806	ATO	Oct 2014	Clinical	0010220792		Aug 2014	Clinical
0010211714	(b) (4)	Nov 2014	Clinical	0010220792		Aug 2014	Clinical
0010218264	ATO	Nov 2014	Clinical	0010220792		Aug 2014	Clinical
0010203492	ATO	Feb 2015	Clinical	0010229668		Nov 2014	Clinical
0010232250	ATO	Mar 2015	Clinical	0010220792 0010229668		Aug 2014 Nov 2014	Clinical Clinical
0010232325	ATO	Mar 2015	Clinical	0010232685		Jan 2015	Clinical
0010232326	ATO	Apr 2015	Clinical	0010232685		Jan 2015	Clinical
0010232327	ATO	Apr 2015	Clinical	0010232685		Jan 2015	Clinical
0010232510	ATO	May 2015	Clinical	0010220792 0010232685		Aug 2014 Jan 2015	Clinical Clinical
0010235955	ATO	Jun 2015	Clinical	0010239533		May 2015	Clinical
0010235965	ATO	Jul 2015	Clinical	0010239533		May 2015	Clinical
0010243325	ATO	Jul 2015	Clinical	0010239533		May 2015	Clinical
0010243326	ATO	Aug 2015	Clinical	0010239533 0010247558		May 2015 May 2015	Clinical Clinical
0010248727	ATO	Aug 2015	Stability	0010247558		May 2015	Clinical
0010266939	ATO	Jan 2016	Stability	0010247558		May 2015	Clinical

(b) (4) ATO = Amgen Thousand Oaks, USA

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^a Additional details of the ABP 980 lots used in the individual clinical studies is provided in [3.2.P.2.3 \(Manufacturing Lot History\)](#).

^b The drug substance lots were manufactured at (b) (4)

Table 2. ABP 980 Lots Included in the Analytical Similarity Assessment (420 mg Presentation)

Drug Product Lot Number	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Drug Product Intended Use ^a	Drug Substance Lot Number	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010163483	ATO	Apr 2014	Clinical, stability	0010200648 ^b	(b) (4)	Nov 2013	Clinical, nonclinical, stability
0010163484	ATO	Jan 2015	Stability	0010229668 ^b		Nov 2014	Clinical
0010264945	ATO	Jan 2016	Stability	0010247558 ^b		May 2015	Clinical
0010295296	ATO	Sep 2016	Development	0010292708 ^b		Feb 2016	Development, stability
0010309515	(b) (4)	Sep 2016	Process validation, Stability	0010253480 ^b		Jul 2015	Process validation
0010309516		Sep 2016	Process validation, Stability	0010262998 ^b		Dec 2015	Validation
0010309517		Sep 2016	Process validation, Stability	0010293548 ^b 0010294000 ^b 0010297878 ^b		May 2016 May 2016 Jun 2016	Process validation, stability Process validation, stability Process validation
0010409768	ADL	Jul 2018	Process Validation	0010383925 ^c		Apr 2018	Process validation
0010412763	ADL	Aug 2018	Process Validation	0010383925 ^c 0010383928 ^c 0010383929 ^c		Apr 2018 Apr 2018 May 2018	Process Validation Process Validation Process Validation
0010412833	ADL	Aug 2018	Process Validation	0010383925 ^c 0010383928 ^c 0010383929 ^c		Apr 2018 Apr 2018 May 2018	Process Validation Process Validation Process Validation

ATO = Amgen Thousand Oaks, USA;

(b) (4)

^a Additional details of the ABP 980 lots used in the individual clinical studies is provided in 3.2.P.2.3 (Manufacturing Lot History).

^b The drug substance lots were manufactured at

(b) (4)

^c The drug substance lots were manufactured at Amgen Rhode Island (ARI).

Table 3. ABP 980 Lots Included in the Analytical Similarity Assessment (Drug Substance)

Drug Substance Lot Number ^b	Drug Substance Manufacturing Site	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010253477	(b) (4)	(b) (4)	Jun 2015	Process validation
0010253479			Jul 2015	Process validation
0010253481			Aug 2015	Process validation, stability
0010253482			Aug 2015	Validation
0010253484			Sep 2015	Validation, LIVCA
0010262996			Sep 2015	Validation
0010262997			Nov 2015	Validation
0010262999			Dec 2015	Validation
0010302656			Aug 2016	Process validation
0010383925	ARI		Apr 2018	Process validation
0010383928	ARI		Apr 2018	Process validation
0010383929	ARI		May 2018	Process validation
0010383930	ARI		May 2018	Process validation
0010383931	ARI		May 2018	Process validation

ARI = Amgen Rhode Island, LIVCA = limit of in vitro cell age study

Reviewer Comment: A total of 47 ABP 980 lots (23 DP lots in 150 mg presentation, 10 DP lots in 420 mg presentation, and 14 DS lots) are included in the updated analytical similarity assessment. As noted in Table 1 to Table 3, the 5 ARI DS validation lots and 3 ADL DP validation lots of ABP 980 are included (marked as yellow).

No new US-licensed Herceptin or EU-approved Herceptin lots were procured for the similarity assessment update. As in the original BLA submission, a total of 23 US-licensed Herceptin lots

and 33 EU-approved Herceptin lots, including all lots used in the clinical studies, were tested as part of the analytical similarity assessment. In the similarity assessment update, additional data were generated for the US-licensed Herceptin 150 mg presentation lots (US 3179410, US 3191001, US 3185091, US 3195644, US 3195645, US 3197057) for the following assays/attributes: potency, HER 2 binding, FcγRIIIa (158F) binding, ADCC by PBMC, FcγRIIIa (131H) binding, C1q binding, SE-UHPLC, rCE-SDS, nrCE-SDS, CEX-HPLC, and reconstituted protein concentration.

Reviewer Comment: A total of 29 lots of US-licensed Herceptin (with expiry date from Jul 2015 to Jun 2021) and 33 lots of EU-approved Herceptin (with expiry date from Feb 2015 to Oct 2019) are included in the updated analytical similarity assessment. The US-licensed Herceptin lots include 23 lots in the original BLA submission on July 28, 2017 and 6 additional lots (US 3179410, US 3191001, US 3185091, US 3195644, US 3195645, US 3197057) submitted in response to the February 8, 2018 IR during the first BLA review cycle together with their NK92 ADCC assay results. The 6 additional lots are 150 mg presentation.

US-licensed Herceptin lots are available in 420 mg (referred to in the submission as 440 mg) and 150 mg presentations. The April 2017 US-Herceptin label change updated the 440 mg multi-use vial to 420 mg multi-dose vial and added a 150 mg single-dose vial, while the reconstitution instructions and the protein concentration upon reconstitution remained unchanged between the 440 mg and 420 mg presentation. EU-approved Herceptin is available in 150 mg presentation. For the 150 mg presentation reconstitution, US-licensed Herceptin label stated to reconstitute with 7.4 mL SWFI (sterile water for injection) while EU-approved Herceptin label stated to reconstitute with 7.2 mL SWFI and the final protein concentration after reconstitution was the same (21 mg/mL).

The Applicant developed ABP 980 with two presentations: 420 mg and 150 mg. The 420 mg presentation was referred as the 440 mg presentation during development. For attributes that are influenced by differences in presentation (e.g., protein content per vial), ABP 980 420 mg and 150 mg presentation was respectively compared with US-licensed Herceptin and EU-approved Herceptin. For attributes that are not influenced by differences in presentation (e.g., protein concentration upon reconstitution, primary structure), the testing results from ABP 980 420 mg and 150 mg presentations were pooled and compared to US-licensed Herceptin and EU-approved Herceptin. The Applicant stated that the data pooling was justified based on the analytical comparability between the ABP 980 420 mg and 150 mg presentations. The Applicant is seeking licensure of the 420 mg presentation.

Testing Design

The following similarity assays were used to address the potential impact resulting from ARI and ADL introduction (table prepared by reviewer):

Category	Assays/Attributes	Tier	Updated number of lots used			Testing facility	Reviewer's Comments
			ABP 980	US	EU		
Biological Activity	Proliferation inhibition bioassay (potency)	1	27	29	33	ATO, AWA	The Applicant addressed the Agency's request of including all biological activity assays/attributes evaluated by an equivalence test or quality ranges in the updated analytical similarity assessment. Lack of CDC was not selected for additional testing based on the Applicant's understanding of lack of CDC activity observed for trastuzumab derived from their own research as well as publications. C1q binding is tested as requested by the Agency.
	HER2 binding by ELISA	2	27	29	33	ATO	
	FcRn binding	2	27	22	33	ATO	
	FcγRIIIa (158V) binding	2	27	29	33	ATO, AWA	
	FcγRIIIa (158F) binding	2	17	20	11		
	NK92 ADCC activity	1	27	29	23		
	PBMC ADCC activity	1	25	27	33		
	FcγRIIa (131H) binding	3	21	19	13		
	C1q binding	3	16	16	10		
Primary Structure	Glycan map: individual species	3	27	29	33	ATO, AWA, ARI, AMA1	The Applicant justifies that sequence variants and key modifications (isomerization, deamidation, oxidation) are included in the DS comparability characterization studies (b) (4) to ARI) and therefore not included in the analytical similarity assessment update. This is acceptable.
	Glycan map: % afucosylation	2					
	Glycan map: % high mannose	2					
	Glycan map: % galactosylation	2					
	Glycan map: % afucosylated galactosylation	2					
	Glycan map: % sialylation	3					
Particles and Aggregates	HIAC: ≥ 2 μm, ≥ 5 μm, ≥ 10 μm, and ≥ 25 μm particles	3	33	6	6	ATO, ADL	-
	SV-AUC: HMW	2	14	9	9	ATO	
Product-related Substances and Impurities	SE-UHPLC	2	16	27	33	ATO, ARI	-
	rCE-SDS	2					
	nrCE-SDS	2					
	CEX-HPLC	2					
General Properties	Protein content	3	32	27	30	ATO, ADL	-
	Reconstituted protein concentration	2					
	Reconstitution time	3	33	3	3	ATO, ADL, Synthon	
Process-related Impurities	HCP ELISA	3	27	3	3	ATO, ARI	-
	Protein A ELISA	3				ATO, AWA, ARI	
	DNA by qPCR	3				ATO, ARI	

HIAC: high accuracy light obscuration particle counting;

SV-AUC: sedimentation velocity-analytical ultracentrifugation

ATO = Amgen Thousand Oaks; AWA = Amgen Washington (the AWA testing labs used for ABP 980 analytical similarity testing are now closed. Data are available at ATO site); AMA1 = Amgen Massachusetts; Synthon = Synthon Biopharmaceuticals BV

Reviewer Comments:

- 1. The Applicant updated the analytical similarity assessment to include ARI and ADL lots in the BLA resubmission. The similarity assays/attributes selected to evaluate impacts of introduction of ARI and ADL ABP 980 lots on similarity assessment were discussed during the Biosimilar Biological Product Development (BPD) Type 1 meeting held on November 30, 2018. In addition to the Applicant's proposed list of similarity assays/attributes (refer to the meeting minutes), the Agency requested that all biological activity assays/attributes evaluated by an equivalence test or quality ranges be conducted on ABP 980 lots produced at the new facilities and included in the updated analytical similarity assessment. The Agency also recommended that the primary structure similarity assessment include a comprehensive assessment of sequence variants and critical post-translational modifications for ABP 980 lots produced at ARI. The Agency also requested the update includes C1q binding and CDC activity results due to differences in C1q binding observed between ABP 980 and US-licensed Herceptin; however, the Agency agreed to review information provided to support a justification for omitting CDC testing from the resubmission provided that C1q binding is evaluated for new ABP 980 lots. From the summary table above, the Applicant addressed the Agency's requests and recommendations regarding similarity assays/attributes selected in the updated analytical similarity assessment, except that comprehensive assessments of sequence variants, certain post-translational modifications, and CDC activities were not included. As indicated in the table above, the Applicant provided justifications for omitting these assays in the analytical similarity assessment update and their justifications are acceptable. The Applicant's considerations regarding manufacturing site transfers and their influences on DS/DP quality attributes included that* (b) (4)

These considerations, together with justifications listed in the above table are adequate to support the Applicant's similarity assays/attributes selected for updating analytical similarity assessment with ARI/ADL lots.

- 2. The method qualifications/verifications for analytical similarity assessment were reviewed during the original review cycle and were considered as suitable for their intended purposes of use. The Applicant's considerations for lot selection for each similarity assessment assay was reviewed in the original review cycle and found to be acceptable.*

The same tier-based similarity assessment as used in the initial BLA applied to the updated analytical similarity assessment. For Tier 1 assays/attributes, an equivalence test was used to establish analytical similarity. For Tier 2 assays/attributes, a quality range (mean $\pm$ 3 SD) was used to establish similarity assessment criteria and the acceptance criteria were considered to be passed when 90% of the test product values passed the reference product quality range. For Tier 3 assays/attributes, a qualitative comparison of the data was performed. All 3 pair-wise comparisons were updated in the analytical similarity assessment update:

- ABP 980 compared to US-licensed Herceptin
- ABP 980 compared to EU-approved Herceptin
- EU-approved Herceptin compared to US-licensed Herceptin

Reviewer Comment: The acceptability of the equivalence test used to support similarity assessment of Tier 1 attributes is deferred to the CMC statistical reviewer.

Results of updated analytical similarity assessment

Reviewer Comment: The updated data for analytical similarity assessment demonstrate that inclusion of ARI and ADL lots does not change the analytical similarity conclusion made during the initial BLA review cycle. No new differences are identified between ABP 980 and US-licensed Herceptin or EU-approved Herceptin. The totality of the analytical data demonstrates the analytical similarity between ABP 980 and US-licensed Herceptin and supports the establishment of the analytical bridge between ABP 980, US-licensed Herceptin, and EU-approved Herceptin to support the use of EU-approved Herceptin as a comparator in clinical studies.

Updated analytical similarity assessment of individual attributes is reviewed as below:

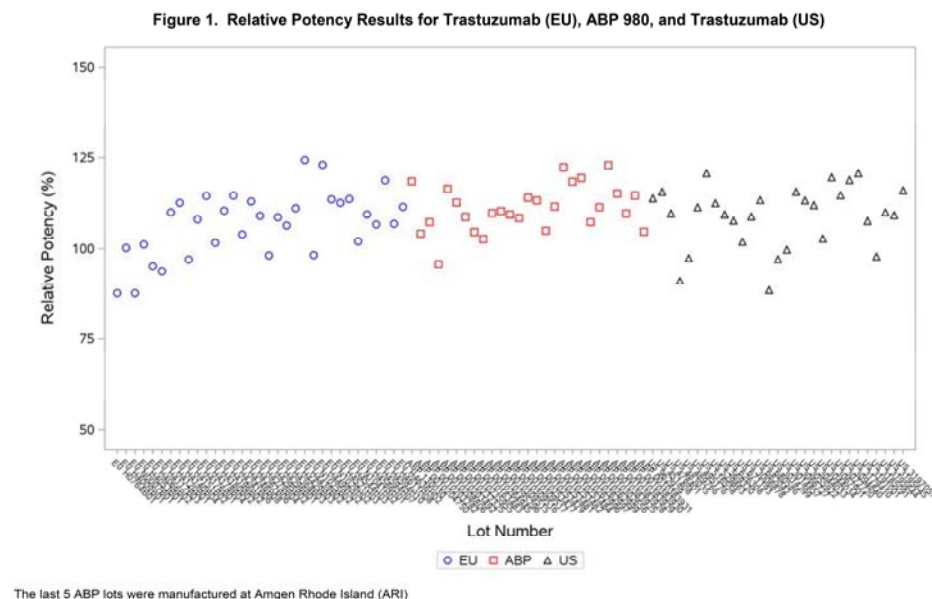
Biological Activity

1. Proliferation Inhibition Bioassay (Potency)

The proliferation inhibition bioassay was performed using a breast cancer cell line (BT-474 cells). The product lots used are summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	29	33	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the proliferation inhibition bioassay in ASA update.
ASA in original BLA submission	22	23	33	

The relative potency results of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are displayed in Figure 1:



The proliferation inhibition bioassay was a tier 1 assay. Equivalence test results performed on the ABP 980 and US-licensed Herceptin lots, APB 980 and EU-approved Herceptin lots, EU-approved Herceptin and US-licensed Herceptin lots are presented in Table 2, Table 3, and Table 4 respectively.

Table 2. Equivalence Test Results for Relative Potency – ABP 980 to Trastuzumab (US)

Assay/Attribute	ABP 980 Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency (%)	111.01	108.83	2.19	-1.17	5.55	±12.89	Equivalent

Table 3. Equivalence Test Results for Relative Potency – ABP 980 to Trastuzumab (EU)

Assay/Attribute	ABP 980 Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency (%)	111.01	106.79	4.23	0.94	7.52	±13.33	Equivalent

Table 4. Equivalence Test Results for Relative Potency – Trastuzumab (EU) to Trastuzumab (US)

Assay/Attribute	Trastuzumab (EU) Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency (%)	106.79	108.83	-2.04	-5.75	1.68	±12.89	Equivalent

Reviewer Comment: Review of the suitability of equivalence tests for the potency assay is deferred to CMC statistical review team in the Office of Biostatistics. The proliferation inhibition bioassay assesses the primary mechanism of action of trastuzumab. The data demonstrate that

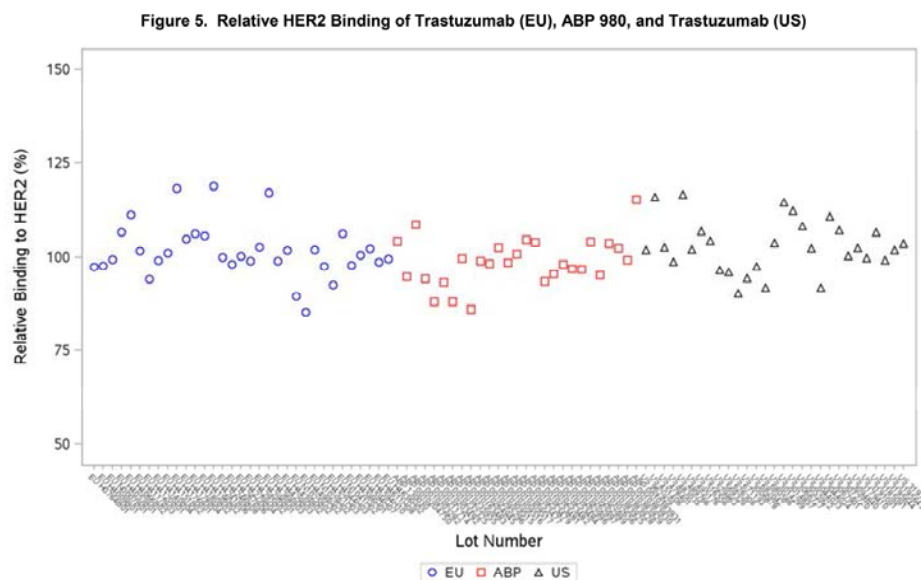
ABP 980 has similar potency compared to US-licensed Herceptin, ABP 980 has similar potency compared to EU-approved Herceptin, and EU-approved Herceptin has similar potency compared to US-licensed Herceptin.

2. HER2 Binding by ELISA

The lots used in HER2 binding by ELISA are summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	29	33	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the HER2 binding by ELISA assay in ASA update.
ASA in original BLA submission	22	23	33	

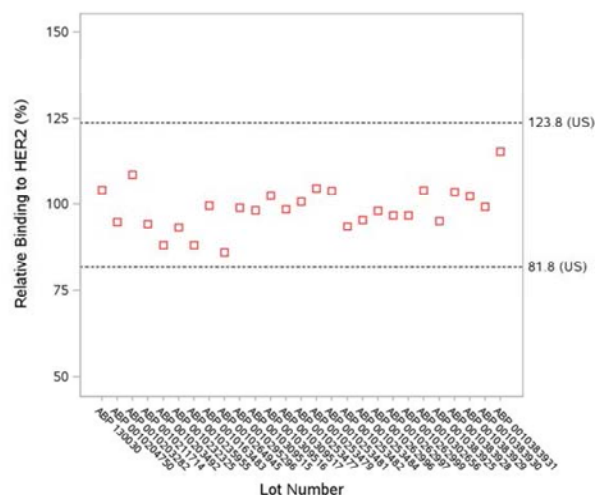
The relative HER2 binding of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are presented in Figure 5.



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

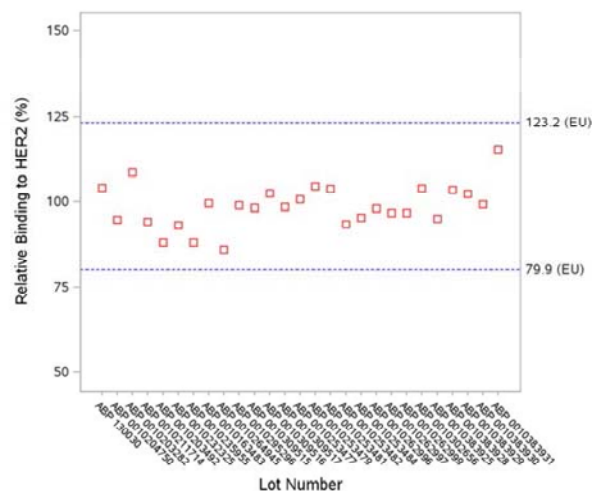
HER2 binding by ELISA was a tier 2 assay. For similarity assessment, all the ABP 980 lots were within the US-licensed Herceptin quality range (Figure 6); all the ABP 980 lots were within the EU-approved Herceptin quality range (Figure 7); and all the EU-approved Herceptin lots were within the US-licensed Herceptin quality range (Figure 8).

Figure 6. Relative Binding to HER2 – ABP 980 Compared to Trastuzumab (US) Quality Range



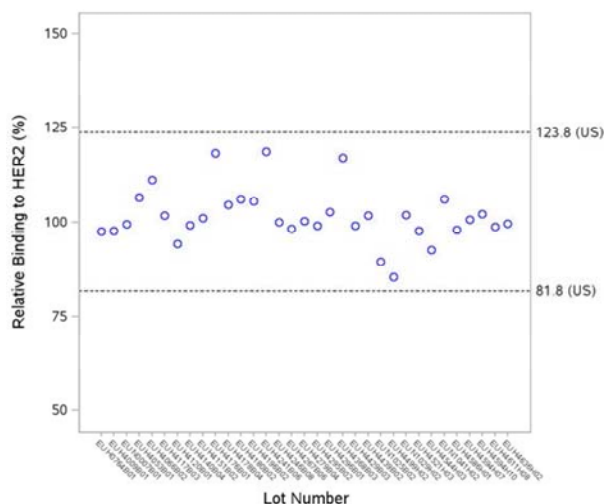
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 7. Relative Binding to HER2 – ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 8. Relative Binding to HER2 – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: The HER2 binding assay is supportive of the primary mechanism of action. The data submitted demonstrate that ABP 980 has similar HER2 binding compared to US-licensed Herceptin, ABP 980 has similar HER2 binding compared to EU-approved Herceptin, and EU-approved Herceptin has similar HER2 binding compared to US-licensed Herceptin.

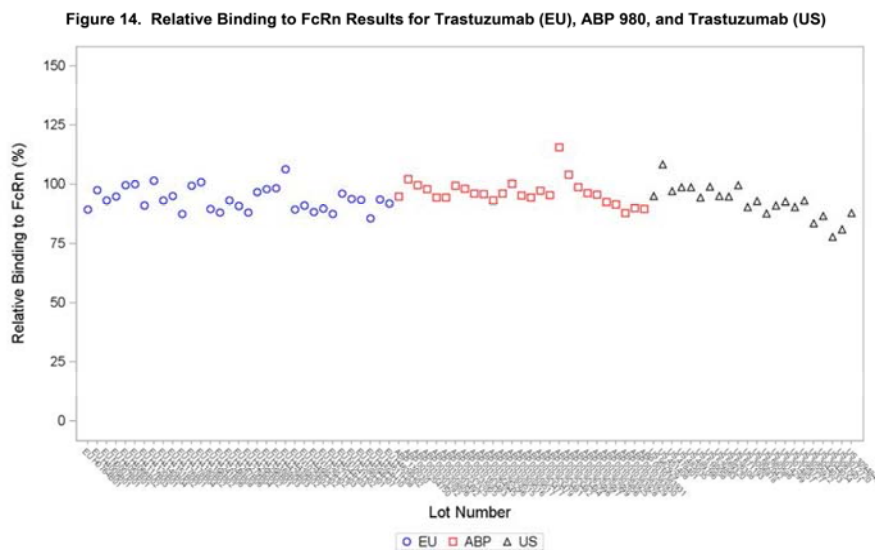
3. FcRn binding

A competitive AlphaScreen[®] binding assay was developed to assess the FcRn binding of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The lots used in FcRn binding assay are summarized in the table below:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP	US-licensed	EU-approved	

	980	Herceptin	Herceptin	
ASA update in BLA resubmission	27	22	33	The 5 ABP 980 ARI DS lots were included in the FcRn binding assay of ASA update.
ASA in original BLA submission	22	22	33	

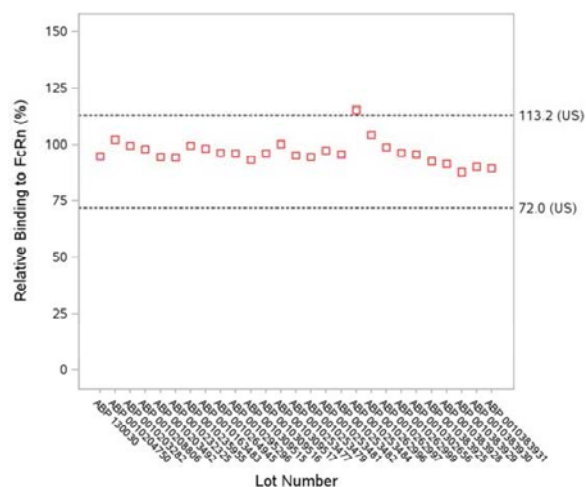
The relative FcRn binding of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are presented in Figure 14:



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

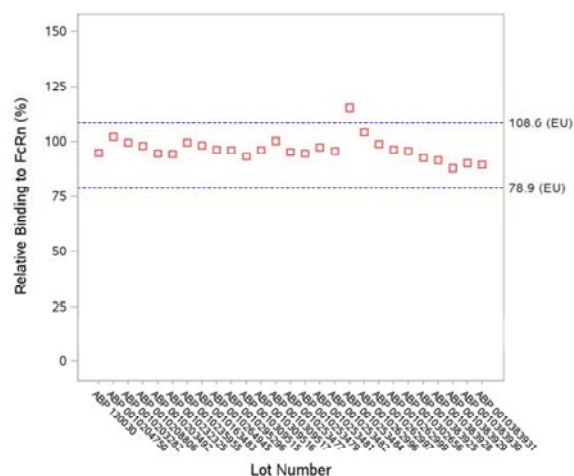
FcRn binding was a tier 2 assay. For similarity assessment, 26 of the 27 ABP 980 lots (96%) were within the US-licensed Herceptin quality range (Figure 15); 26 of the 27 ABP 980 lots (96%) were within the EU-approved Herceptin quality range (Figure 16); and all the EU-approved Herceptin lots were within the US-licensed Herceptin quality range (Figure 17).

Figure 15. Relative Binding to FcRn – ABP 980 Compared to Trastuzumab (US) Quality Range



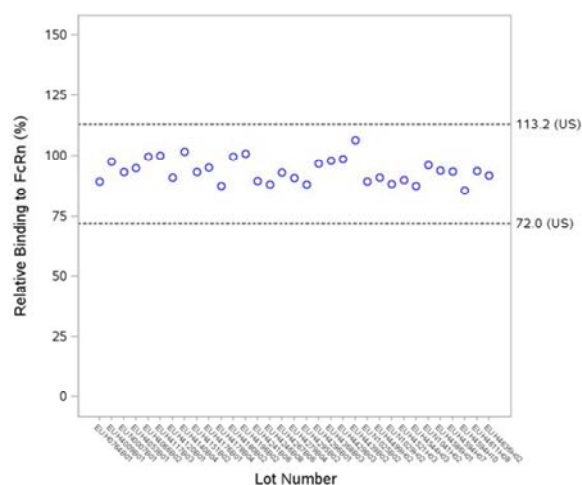
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 16. Relative Binding to FcRn – ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 17. Relative Binding to FcRn – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: FcRn binding impacts IgG PK. The results demonstrate that ABP 980 has similar FcRn binding compared to US-licensed Herceptin, ABP 980 has similar FcRn binding compared to EU-approved Herceptin, and EU-approved Herceptin has similar FcRn binding compared to US-licensed Herceptin.

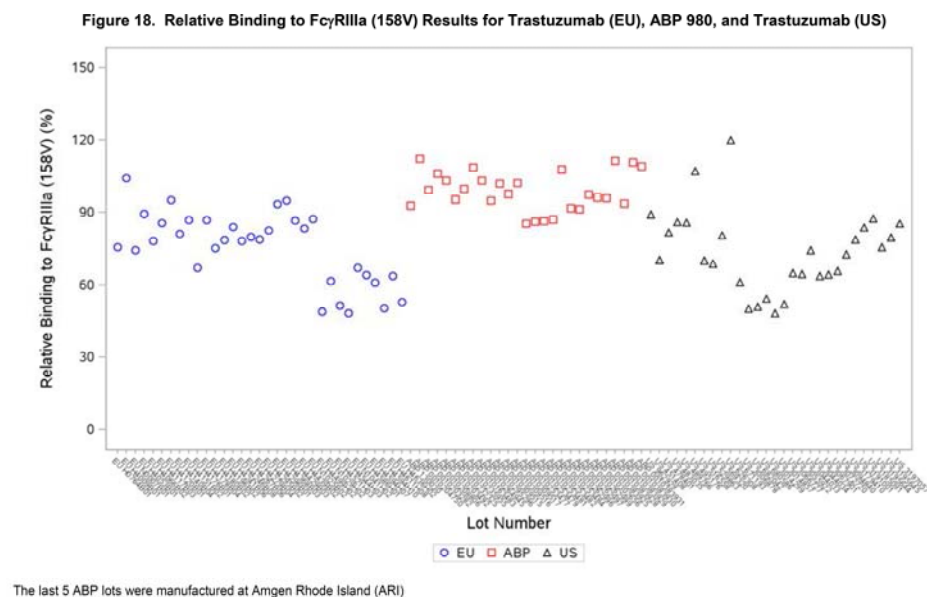
4. FcγRIIIa (158V) Binding

A competitive AlphaLISA[®] binding assay was developed to assess the binding of FcγRIIIa (158V) to ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Lots used in FcγRIIIa (158V) binding are summarized in the following table:

Analytical Similarity	Number of lots used	Notes
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Assessment (ASA)	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	29	33	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the FcγRIIIa (158V) binding assays in ASA update.
ASA in original BLA submission	22	23	33	

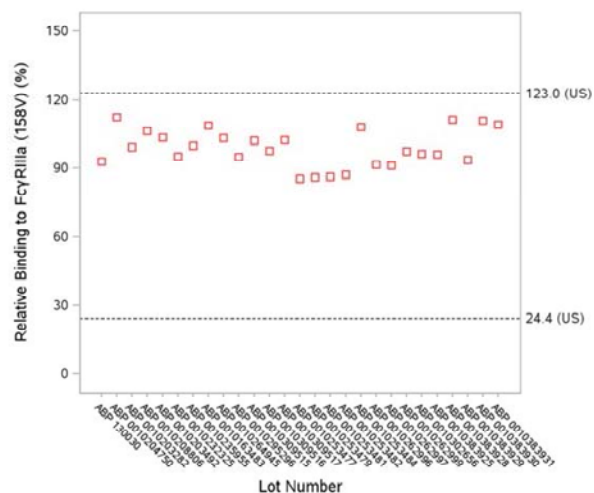
The FcγRIIIa (158V) binding activity of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are presented in Figure 18:



Reviewer Comment: From Figure 18, the US-licensed Herceptin and EU-approved Herceptin lots show relatively wide ranges of FcγRIIIa (158V) binding activity, which are consistent with the wide ranges observed for FcγRIIIa (158F) binding, glycan profiles, and ADCC activities (see following sections). The relatively low FcγRIIIa (158V) binding levels observed in certain US-licensed Herceptin and EU-approved Herceptin lots are attributed to lower levels of afucosylation, afucosylated galactosylation, and galactosylation. These same US-licensed Herceptin and EU-approved Herceptin lots also have relatively low FcγRIIIa (158F) binding, and ADCC activity.

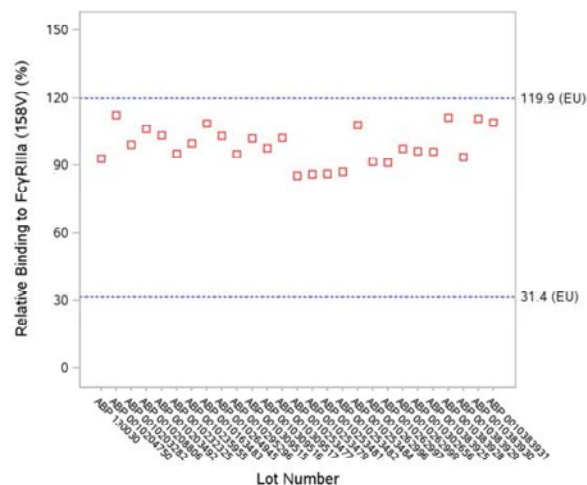
FcγRIIIa (158V) binding was a tier 2 assay. For similarity assessment, all ABP 980 lots were within US-licensed Herceptin quality range (Figure 20); all ABP 980 lots were within EU-approved Herceptin quality range (Figure 21); all EU-approved Herceptin lots were within US-licensed Herceptin quality range (Figure 22).

Figure 20. Relative Binding to FcγRIIIa (158V) – ABP 980 Compared to Trastuzumab (US) Quality Range



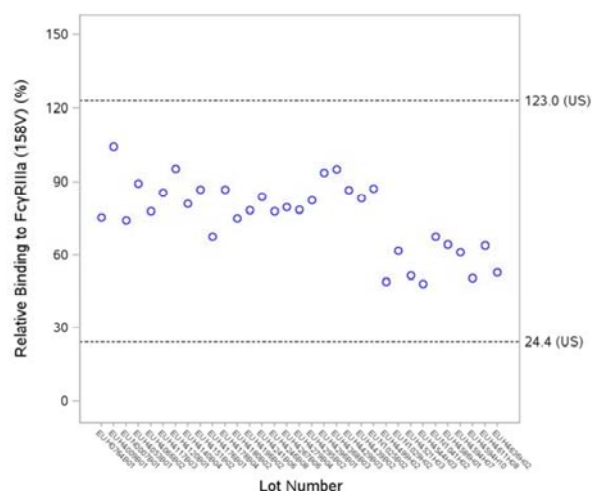
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 21. Relative Binding to FcγRIIIa (158V) – ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 22. Relative Binding to FcγRIIIa (158V) – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: FcγRIIIa (158V) binding is orthogonal to ADCC in assessing the biological property of Fc-mediated function. The results demonstrate that ABP 980 has similar FcγRIIIa (158V) binding compared to US-licensed Herceptin, ABP 980 has similar FcγRIIIa (158V) binding compared to EU-approved Herceptin, and EU-approved Herceptin has similar FcγRIIIa (158V) binding compared to US-licensed Herceptin.

5. FcγRIIIa (158F) binding

A competitive AlphaLISA[®] binding assay was used to assess the binding of FcγRIIIa (158F) to ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Lots used in FcγRIIIa (158F) binding are summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Notes
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	17	20	11	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the FcγRIIIa (158F) binding assay in ASA update.
ASA in original BLA submission	12	14	11	

FcγRIIIa (158F) binding was a tier 2 assay. For similarity assessment, all ABP 980 lots were within US-licensed Herceptin quality range; all ABP 980 lots were within EU-approved Herceptin quality range; all EU-approved Herceptin lots were within US-licensed Herceptin quality range.

Reviewer Comment: Binding to FcγRIIIa high affinity variant (158V) and low affinity variant (158 F) is orthogonal to ADCC in assessing the biological property of Fc-mediated function. The results demonstrate that ABP 980 has similar FcγRIIIa (158F) binding compared to US-licensed Herceptin, ABP 980 has similar FcγRIIIa (158F) binding compared to EU-approved Herceptin, and EU-approved Herceptin has similar FcγRIIIa (158F) binding compared to US-licensed Herceptin.

6. ADCC activity (ADCC using NK92 Cells and ADCC using PBMC)

Lots used in NK92 ADCC assays and PBMC ADCC assays are summarized in the following table. Both NK92 and PBMC ADCC assays are tier 1 assays.

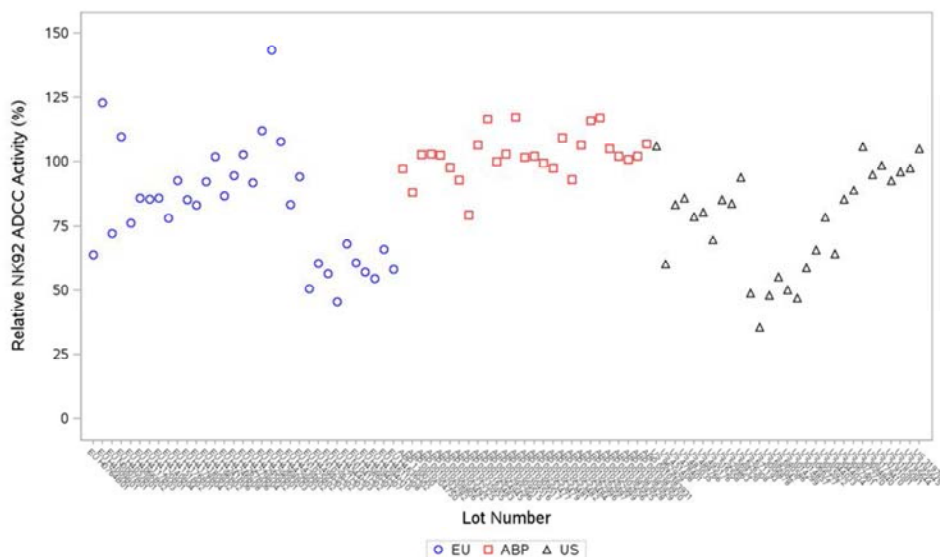
Analytical Similarity Assessment (ASA)	Number of lots used						Note
	NK92 ADCC assay			PBMC ADCC assay			
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	29	33	25	27	33	For NK92 ADCC assay, 5 ABP 980 ARI DS lots were included in the ASA update; for PBMC ADCC assay, 3 ABP 980 ARI DS lots and 4 US-licensed Herceptin 150 mg presentation lots were included in the ASA update.
ASA in original BLA submission	22	29	33	22	23	33	

ADCC using NK92 Cell

An NK92 cell line engineered to express high affinity variant of FcγRIIIa (158V) was used as the effector cell, and HER2-expressing HCC2218 was used as target cells for NK92 ADCC assay. The relative NK92 ADCC activity results of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are presented in Figure 29. Low values of NK92 ADCC activity were observed for certain US-licensed Herceptin and EU-approved Herceptin batches as shown in Figure 29. This

observation was correlated with glycan distributions and FcγRIIIa binding data observed for the same lots.

Figure 29. Relative NK92 ADCC Activity Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

The equivalence test results are presented in Table 12 (ABP 980 to US-licensed Herceptin), Table 13 (ABP 980 to EU-approved Herceptin), and Table 14 (EU-approved Herceptin to US-licensed Herceptin). For comparison of ABP 980 and US-licensed Herceptin, the upper bound of 90% confidence interval (CI) exceeded the EAC (Table 12). For comparison of ABP 980 and EU-approved Herceptin, and comparison of EU-approved Herceptin and US-licensed Herceptin, the confidence bounds on the difference in means fell within the EAC.

Table 12. Equivalence Test Results for Relative NK92 ADCC – ABP 980 to Trastuzumab (US)

Assay/Attribute	ABP 980 Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC activity (%)	102.53	77.41	25.12	18.20	32.04	±30.32	Not Equivalent

Table 13. Equivalence Test Results for Relative NK92 ADCC – ABP 980 to Trastuzumab (EU)

Assay/Attribute	ABP 980 Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC activity (%)	102.53	82.70	19.83	12.71	26.96	±33.60	Equivalent

Table 14. Equivalence Test Results for Relative NK92 ADCC – Trastuzumab (EU) to Trastuzumab (US)

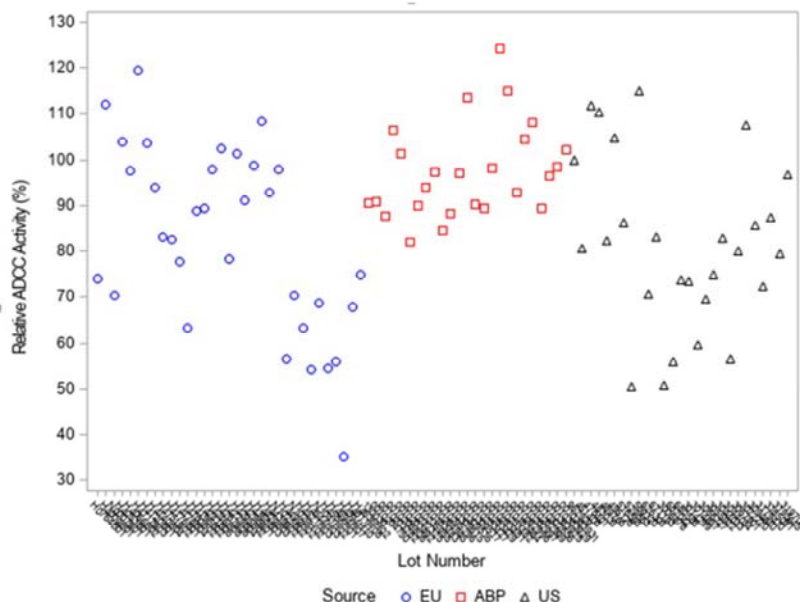
Assay/Attribute	Trastuzumab (EU) Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC activity (%)	82.70	77.41	5.29	-3.75	14.33	±30.32	Equivalent

Reviewer Comment: The NK92 ADCC assay results demonstrate that ABP 980 has similar ADCC activity compared to EU-approved Herceptin, and EU-approved Herceptin has similar ADCC activity compared to US-licensed Herceptin. The observation that the statistical equivalence criteria for NK92 ADCC assay was not met when ABP 980 was compared to US-licensed Herceptin complies with the observation during original BLA review cycle. To further evaluate the similarity of ADCC activity, the Applicant performed PBMC ADCC assay and the PBMC ADCC assay results met the statistical equivalence criteria (see following section). Furthermore, quality attributes that are tightly linked to ADCC activity, such as HER2 binding, FcγRIIIa binding, afucosylation, are demonstrated as similar between ABP 980 and US-licensed Herceptin. The updated results do not change the conclusion from the first review cycle that totality of evidence supports the conclusion that differences observed in NK92 ADCC activity do not preclude a determination of high similarity between ABP 980 and US-licensed Herceptin.

ADCC using PBMC

In addition to NK92 ADCC assay, a second ADCC assay using peripheral blood mononuclear cells (PBMC) as effector cells was performed to evaluate ADCC similarity. The relative PBMC ADCC results of EU-approved Herceptin, ABP 980, and US-licensed Herceptin are presented in Figure 34.

Figure 34. Relative PBMC ADCC Activity Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Rhode Island (ARI)

The equivalence test results are presented in Table 16 (ABP 980 to US-licensed Herceptin), Table 17 (ABP 980 to EU-approved Herceptin), and Table 18 (EU-approved Herceptin to US-licensed Herceptin). The confidence bounds on the difference in means fell within the EAC for all three comparisons.

Table 16. Equivalence Test Results for Relative PBMC ADCC – ABP 980 to Trastuzumab (US)

Assay/Attribute	ABP 980 Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	97.30	81.58	15.72	8.81	22.64	±27.78	Equivalent

Table 17. Equivalence Test Results for Relative PBMC ADCC – ABP 980 to Trastuzumab (EU)

Assay/Attribute	ABP 980 Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	97.30	82.76	14.54	7.79	21.30	± 29.93	Equivalent

Table 18. Equivalence Test Results for Relative PBMC ADCC – Trastuzumab (EU) to Trastuzumab (US)

Assay/Attribute	Trastuzumab (EU) Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	82.76	81.58	1.18	-7.14	9.5	±27.78	Equivalent

Reviewer Comment: The PBMC ADCC assay results demonstrate that ABP 980 has similar ADCC activity compared to US-licensed Herceptin, ABP 980 has similar ADCC activity compared to EU-approved Herceptin, and EU-approved Herceptin has similar ADCC activity compared to US-licensed Herceptin.

7. FcγRIIa (131H) Binding

A competitive AlphaLISA binding assay was developed to assess the FcγRIIa (131H) binding with ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Information of product lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	21	19	13	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the FcγRIIa (131H) binding assay in ASA update.
ASA in original BLA submission	16	13	13	

FcγRIIa (131H) binding with IgG elicits ADCP. The Applicant stated that the ADCP contribution to clinical efficacy of trastuzumab and the relevance of FcγRIIa binding to trastuzumab clinical efficacy were not clear, therefore the FcγRIIa (131H) binding was a Tier 3 assay. The assay results showed similar FcγRIIa (131H) binding activity between ABP 980 and US-licensed Herceptin, between ABP 980 and EU-approved Herceptin, between EU-approved Herceptin and US-licensed Herceptin.

8. C1q Binding

The C1q binding activity was tested using ELISA. Information of product lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	16	16	10	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the C1q binding assay in ASA update.
ASA in original BLA submission	11	10	10	

Due to absence of CDC activity for trastuzumab, C1q binding was classified as a tier 3 assay. From the C1q binding results (Table 20), ABP 980 showed relatively higher C1q binding than US-licensed Herceptin and EU-approved Herceptin, while the C1q binding results of US-licensed Herceptin and EU-approved Herceptin were similar. The lots marked as yellow are the lots added to the similarity assessment update.

Table 20. C1q Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	Relative C1q Binding (%)	Lot Number	Relative C1q Binding (%)	Lot Number	Relative C1q Binding (%)
EU H0764B01	79	ABP 130030	101	US 962929	100
EU H4009B01	101	ABP 0010204750	98	US 516558	96
EU H4053B01	94	ABP 0010203282	107	US 529863	87
EU H4066B02	90	ABP 0010208806	107	US 626308	108
EU H4246B08	88	ABP 0010203492	108	US 671193	98
EU H4521H03	72	ABP 0010232325	118	US 3014299	85
EU H4544H03	74	ABP 0010235955	112	US 3014857	89
EU N1041H02	92	ABP 0010163483	118	US 3055922	92
EU H4586H01	90	ABP 0010309515	109	US 3044033	83
EU H4594H07	102	ABP 0010309516	134	US 3072720	107
		ABP 0010309517	124	US 3179410	99
		ABP 0010383925	110	US 3191001	104
		ABP 0010383928	146	US 3185091	95
		ABP 0010383929	139	US 3195644	101
		ABP 0010383930	150	US 3195645	99
		ABP 0010383931	146	US 3197057	90
EU mean	88	ABP mean	120	US mean	96
EU SD	10	ABP SD	17	US SD	8
EU min to max range	72 to 102	ABP min to max range	98 to 150	US min to max range	83 to 108

The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Reviewer Comment: Given that CDC activity is absent for trastuzumab, the minor C1q binding differences observed would not preclude determination of similarity of ABP 980 to US-licensed Herceptin or the adequacy of the analytical bridge.

Primary Structure

Glycan Map

Information of lots used in glycan map study is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	29	33	The 5 ABP 980 ARI DS lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the glycan map analysis of analytical similarity assessment update.
ASA in original BLA submission	22	23	33	

The following glycan groups were evaluated as part of the similarity assessment: afucosylation, high mannose, galactosylation, afucosylated galactosylation, and sialylation. The contents of each glycan group for the three products are presented in Figure 10 (afucosylation), Figure 11 (high mannose), Figure 12 (galactosylation), Figure 13 (afucosylated galactosylation), and Figure 14 (sialylation).

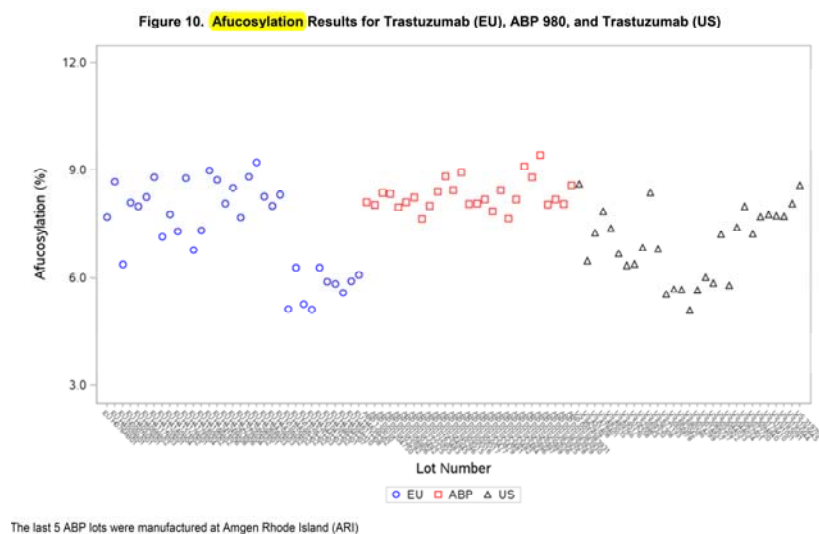
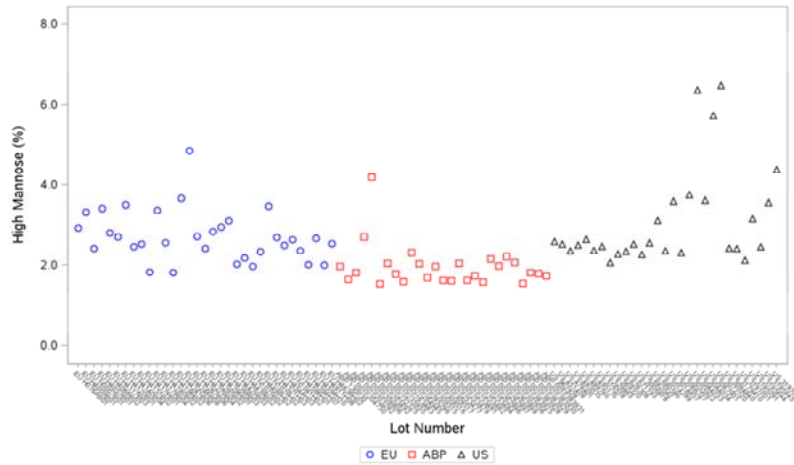
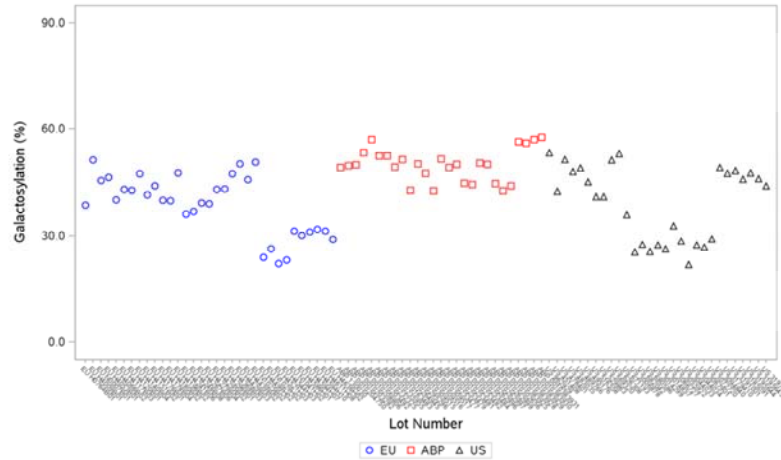


Figure 11. **High Mannose** Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



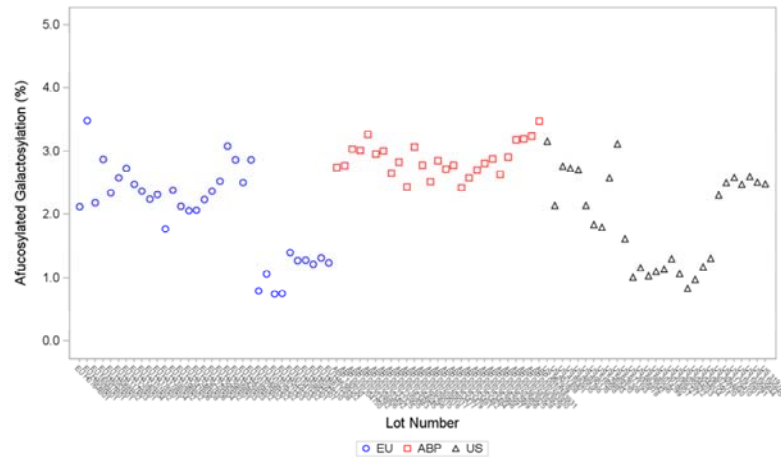
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 12. **Galactosylation** Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



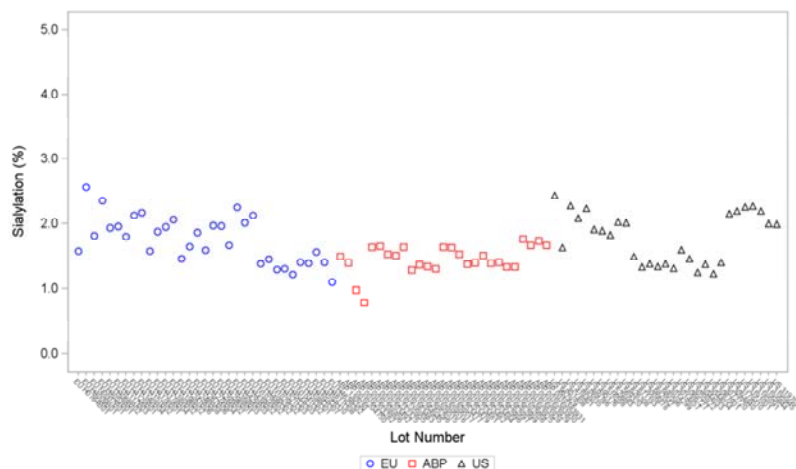
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 13. **Afucosylated Galactosylation** Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 14. Sialylation Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

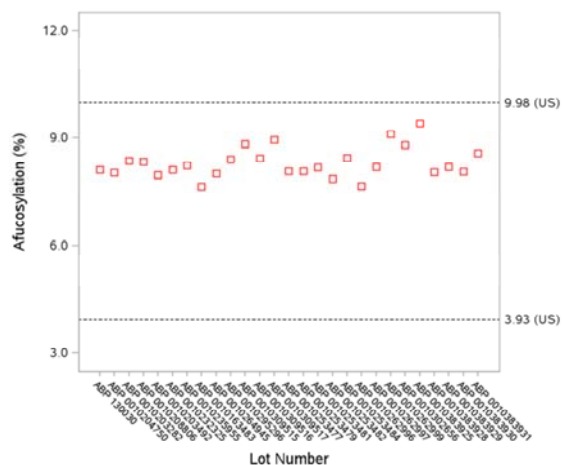


The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Reviewer Comment: As discussed above, certain EU-approved Herceptin and US-licensed Herceptin lots show decreased levels of afucosylation, galactosylation, and afucosylated galactosylation, which are consistent with results observed in FcγRIIIa binding and ADCC activity.

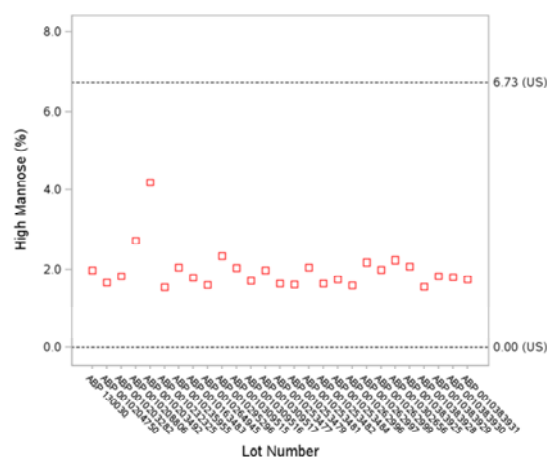
Afucosylated species impact ADCC activity; high mannose species may impact PK and ADCC; galactosylated species may impact ADCC; afucosylated-galactosylated species impact ADCC. Therefore, these attributes were classified as tier 2 attribute. Tier 2 glycan results of all the ABP 980 lots were within the quality range of US-licensed Herceptin lots (Figure 15 to 18) and EU-approved Herceptin lots (Figure 19 to 22), and results of EU-approved Herceptin lots were all within the quality range of US-licensed Herceptin lots (Figure 23 to 26). Sialylation has a low potential to impact ADCC, therefore was classified as tier 3 attribute. For sialylation, qualitative data comparison showed that ABP 980 lots had similar sialylation levels as US-licensed Herceptin and EU-approved Herceptin lots, and EU-approved Herceptin lots had similar sialylation levels as US-licensed Herceptin lots.

Figure 15. Afucosylation- ABP 980 Compared to Trastuzumab (US) Quality Range



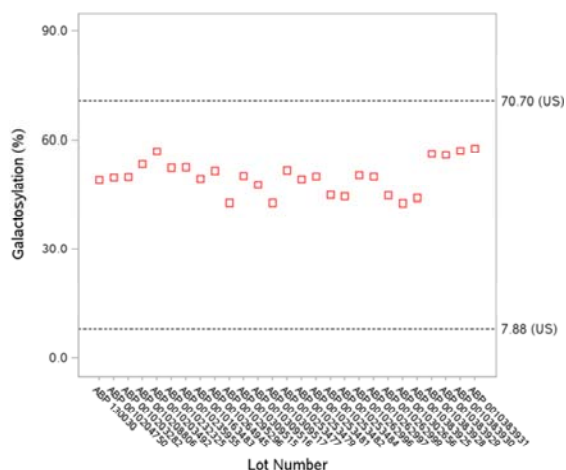
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 16. High Mannose - ABP 980 Compared to Trastuzumab (US) Quality Range



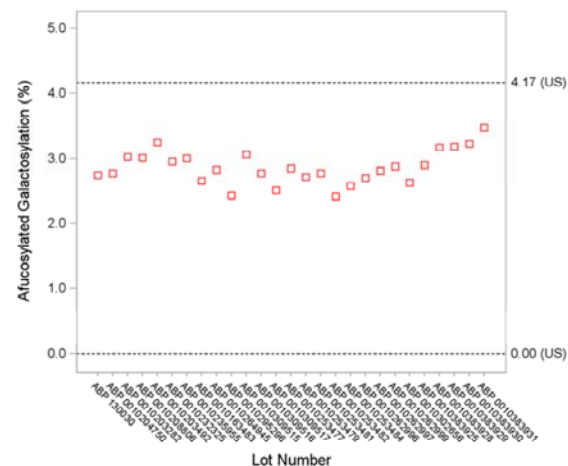
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 17. Galactosylation - ABP 980 Compared to Trastuzumab (US) Quality Range



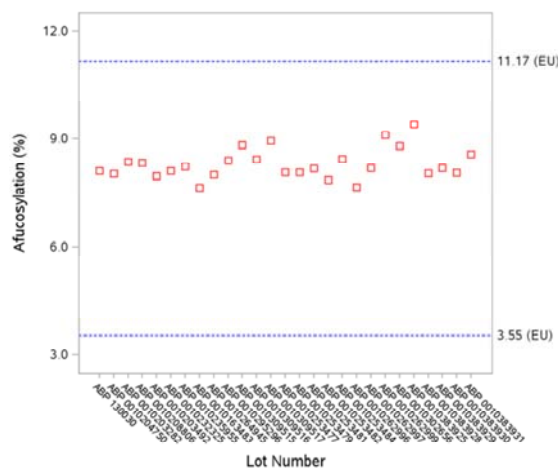
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 18. Afucosylated Galactosylation - ABP 980 Compared to Trastuzumab (US) Quality Range



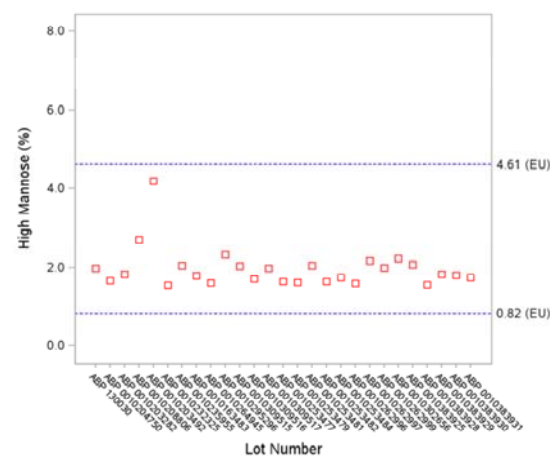
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 19. Afucosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range



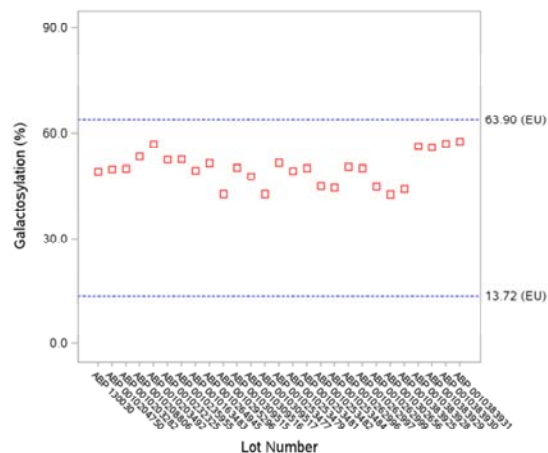
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 20. High Mannose - ABP 980 Compared to Trastuzumab (EU) Quality Range



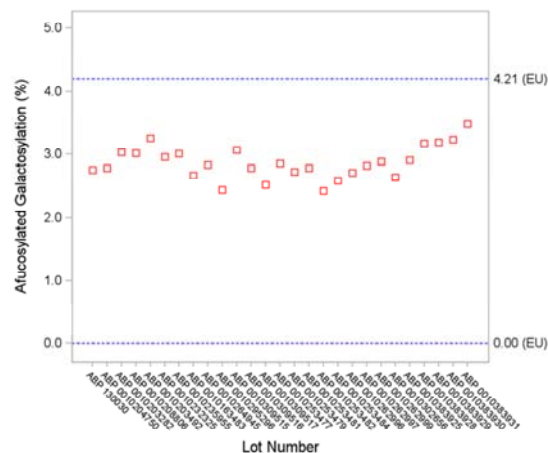
The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 21. Galactosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 22. Afucosylated Galactosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 5 ABP lots were manufactured at Amgen Rhode Island (ARI)

Figure 23. Afucosylation - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range

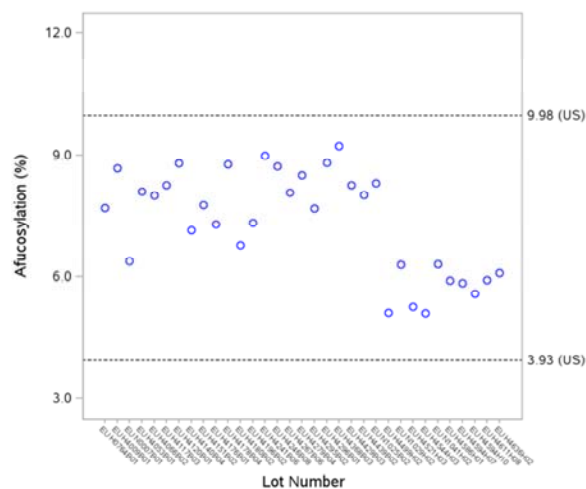


Figure 24. High Mannose - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range

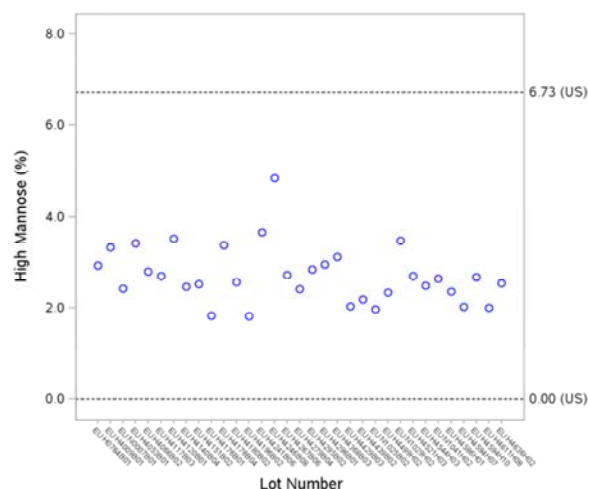


Figure 25. Galactosylation - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range

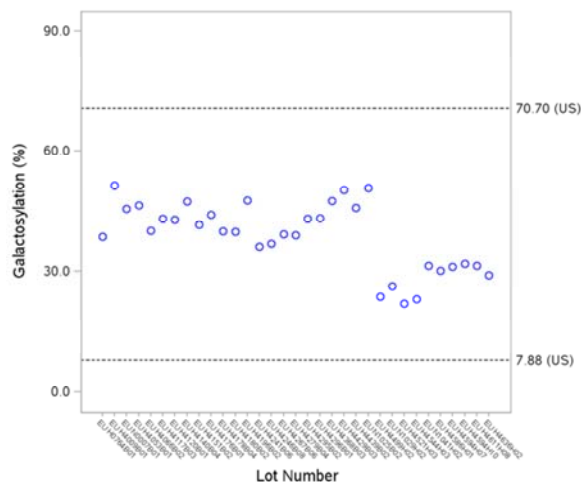
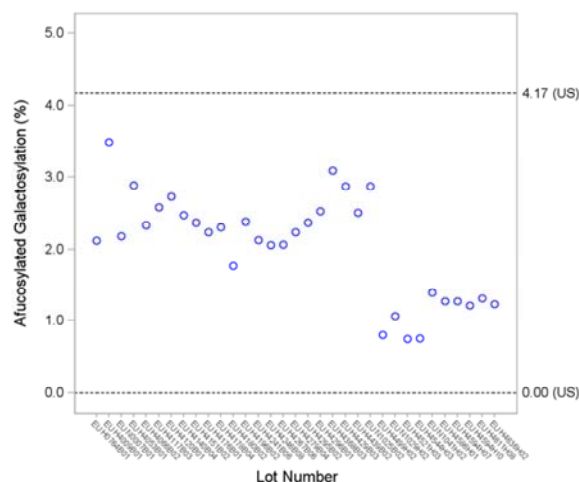


Figure 26. Afucosylated Galactosylation – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: The glycan map data show that ABP 980 lots have similar levels of afucosylation, high mannose, galactosylation, afucosylated galactosylation, and sialylation as compared to EU-approved Herceptin and US-licensed Herceptin lots. EU-approved Herceptin lots have similar levels of afucosylation, high mannose, galactosylation, afucosylated galactosylation, and sialylation as compared to US-licensed Herceptin lots.

Particles and Aggregates

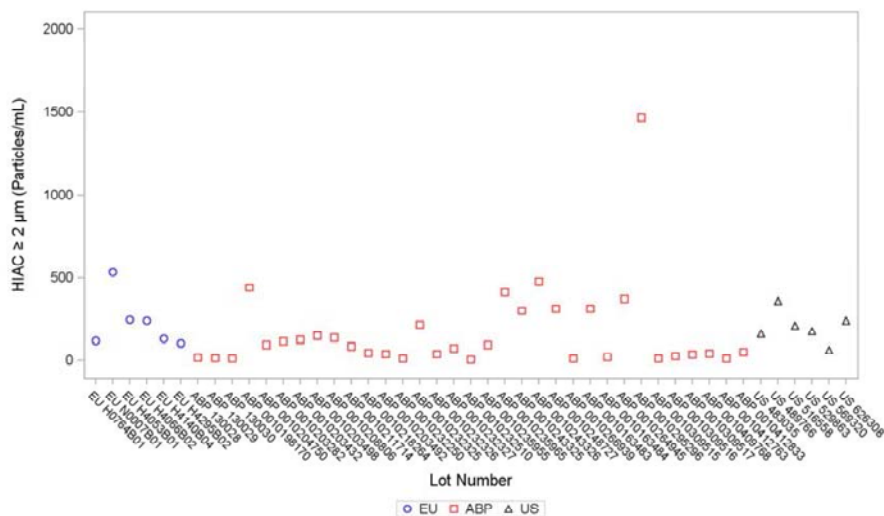
HIAC

Light obscuration (HIAC) was used to evaluate the subvisible particles ($\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$) in the DP lots and was classified as tier 3 assay. Information of lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	33	6	6	The 3 ABP 980 ADL DP lots were included in the HIAC assay in analytical similarity assessment update.
ASA in original BLA submission	30	6	6	

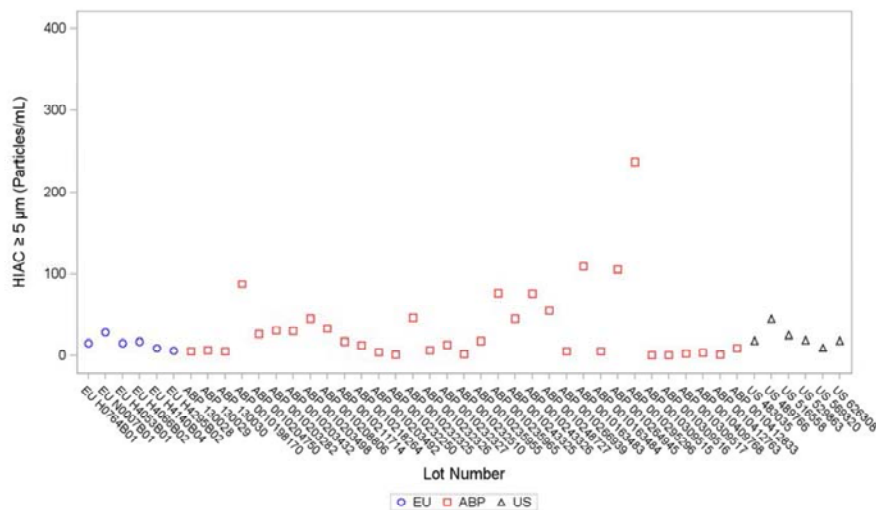
The HIAC results in terms of $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ subvisible particles are presented in Figure 1 to Figure 4:

Figure 1. HIAC $\geq 2 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



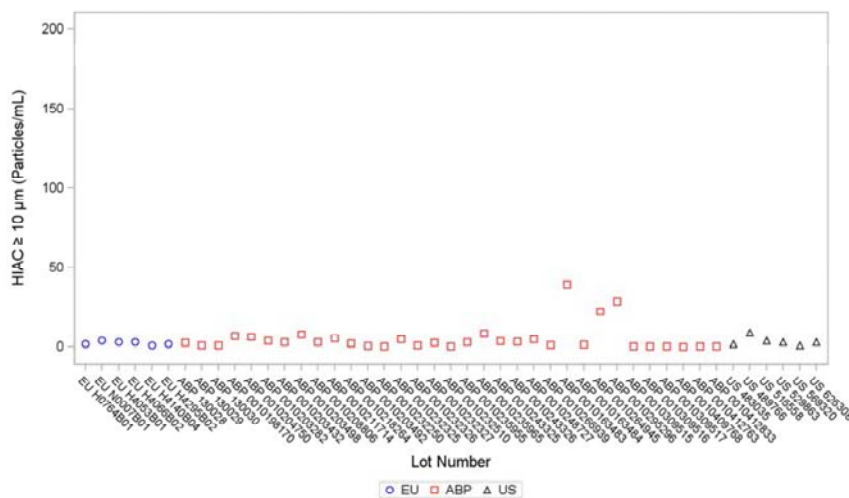
The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 2. HIAC $\geq 5 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



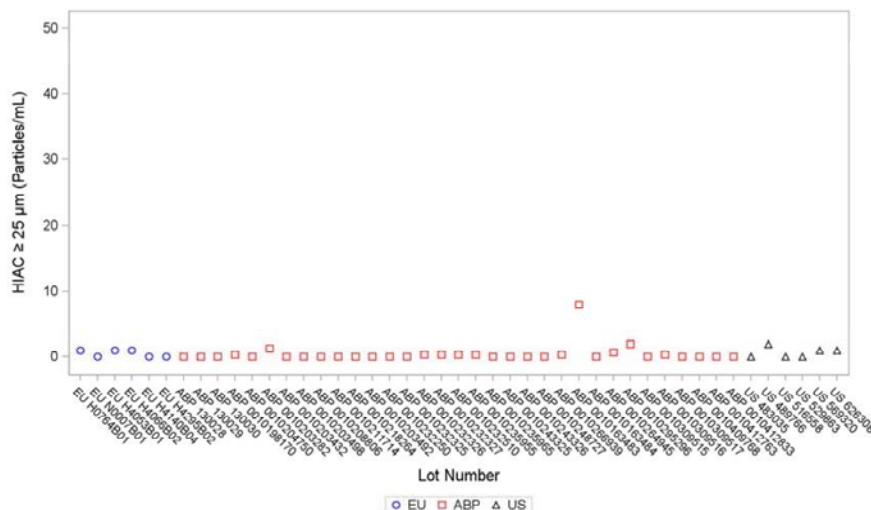
The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 3. HIAC $\geq 10 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 4. HIAC $\geq 25 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Reviewer Comment: The HIAC results show that the overall levels of subvisible particles for samples of ABP 980, EU-approved Herceptin and US-licensed Herceptin are well within the limits of USP and PhEur. Certain ABP 980 lots show relatively higher levels of sub-visible particles, but the differences may be attributable to method variability and sample size. Since the overall levels of subvisible particles are low, the differences observed are unlikely to have an adverse impact on safety. Overall, the HIAC data support the conclusion that the three products have similar levels of sub-visible particles across all size ranges tested.

SV-AUC: HMW

Analytical ultracentrifugation sedimentation velocity (SV-AUC) measures the distribution and %concentration of HMW species of the product in solution. Level of SV-AUC HMW species was classified as tier 2 attribute. Information of lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	14*	9	9	* The 3 ABP 980 ADL DP lots were included in the SV-AUC assay in ASA update. SV-AUC profiles of the 3 ADL DP lots were provided in section 3.2.P.2.3 Product Comparability – Actavis to ADL, 420 mg
ASA in original BLA submission	11	9	9	

The HMW species levels were below the method limit of quantitation (LOQ = 3.7%) for all samples tested.

Reviewer Comment: The SV-AUC results demonstrate similar SV-AUC profiles and similar HMW species levels (below method LOQ) between ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

Product-related Substances and Impurities

A combination of methods was used to assess product-related substances and impurities. Size variants were assessed by SE-UHPLC, rCE-SDS, and nrCE-SDS. Charge variants were assessed by CEX-HPLC. Information of lots used for product-related substances and impurities analysis is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	16	27	33	The 3 ABP 980 ADL DP lots and 6 US-licensed Herceptin 150 mg presentation lots were included in the product-related substances and impurities analysis of ASA update.
ASA in original BLA submission	13	21	33	

SE-UHPLC (% HMW, % main peak), rCE-SDS (% HC+LC, % LMW + HMW, % NGHC), nrCE-SDS (% main peak, % pre-peaks), CEX-HPLC (% acidic peaks, % main peak, % basic peaks) were considered tier 2 attributes. For attributes that change over time (main peak and HMW by SE-UHPLC, main peak and basic peaks by CEX-HPLC), quality range tests were performed on both age-adjusted and non-age-adjusted (first time point) results.

SE-UHPLC (% HMW, % main peak)

The quality range tests based on age-adjusted results showed that:

- 1) 100% ABP 980 lots fell within the US-licensed Herceptin quality range of HMW (Figure 7), and 88% (14 of the 16) ABP 980 lots fell within the US-licensed Herceptin quality range of main peak (Figure 8);
- 2) 25% (4 of the 16) ABP 980 lots fell within the EU-approved Herceptin quality range of HMW (Figure 9), and 6% (1 of the 16) ABP 980 lots fell within the EU-approved Herceptin quality range of main peak (Figure 10);
- 3) 100% EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of HMW and main peak.

Figure 7. SE-UHPLC HMW - ABP 980 Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range

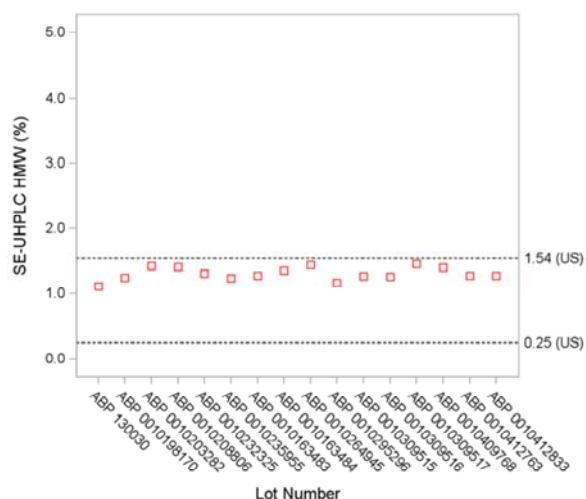


Figure 8. SE-UHPLC Main Peak – ABP 980 Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range

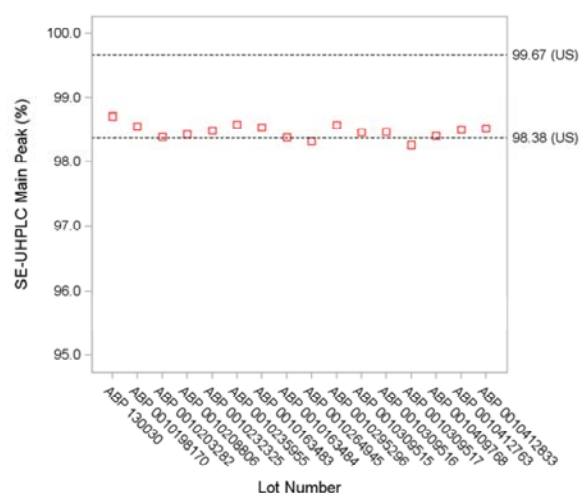


Figure 9. SE-UHPLC HMW - ABP 980 Age-adjusted Values Compared to Trastuzumab (EU) Age-adjusted Quality Range

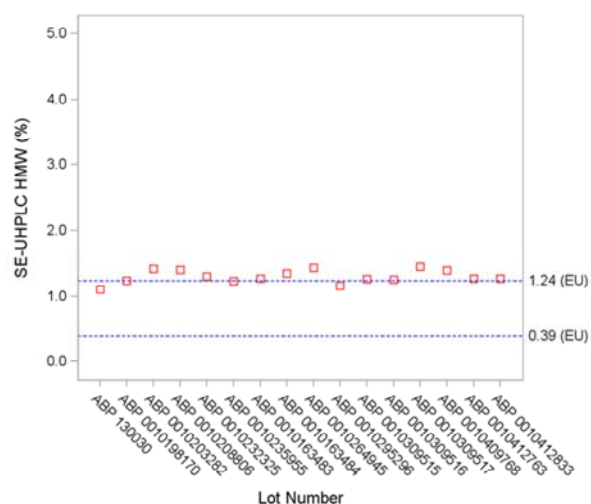
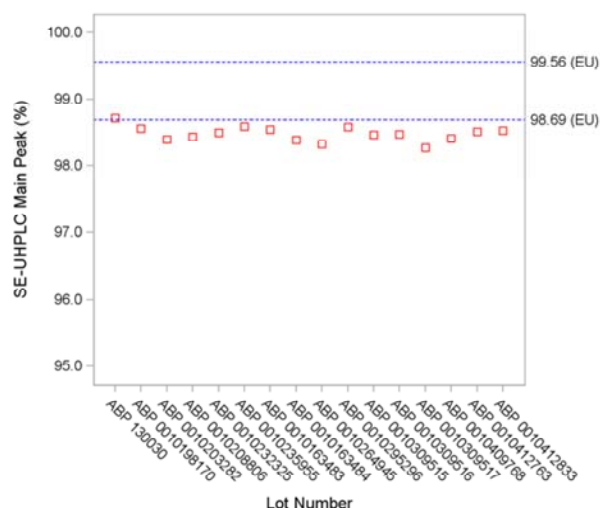


Figure 10. SE-UHPLC Main Peak - ABP 980 Age-adjusted Values Compared to Trastuzumab (EU) Age-adjusted Quality Range



The non-age-adjusted results of SE-HPLC HMW and main peak are presented in Figure 90 and Figure 91 respectively. The quality range tests based on non-age-adjusted results showed that:

- 1) 100% ABP 980 lots fell within the US-licensed Herceptin quality range of HMW, and 94% (15 of the 16) ABP 980 lots fell within the US-licensed Herceptin quality range of main peak;
- 2) 100% ABP 980 lots fell within the EU-approved Herceptin quality range of HMW, and 94% (15 of the 16) ABP 980 lots fell within the EU-approved Herceptin quality range of main peak;
- 3) 100% EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of HMW and main peak, respectively.

Figure 90. SE-UHPLC HMW Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US) First Time Point Analysis

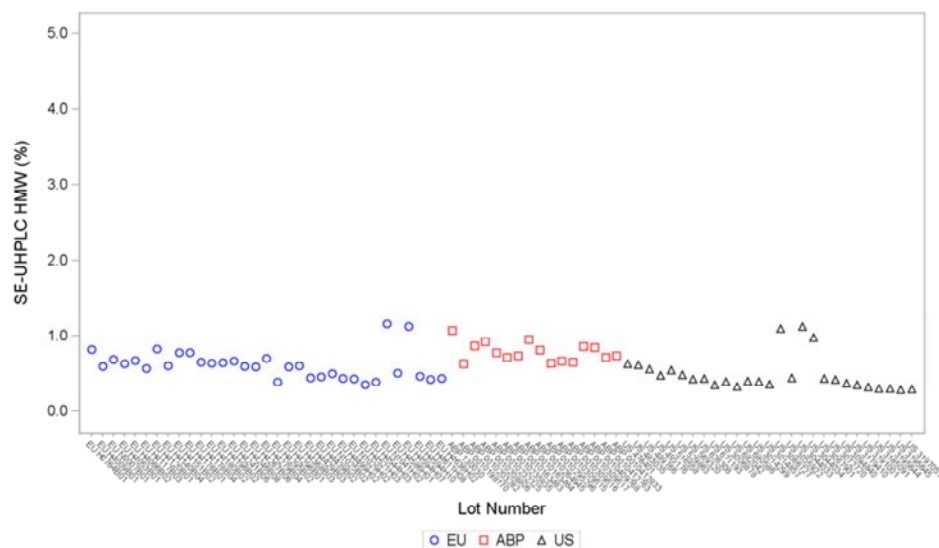
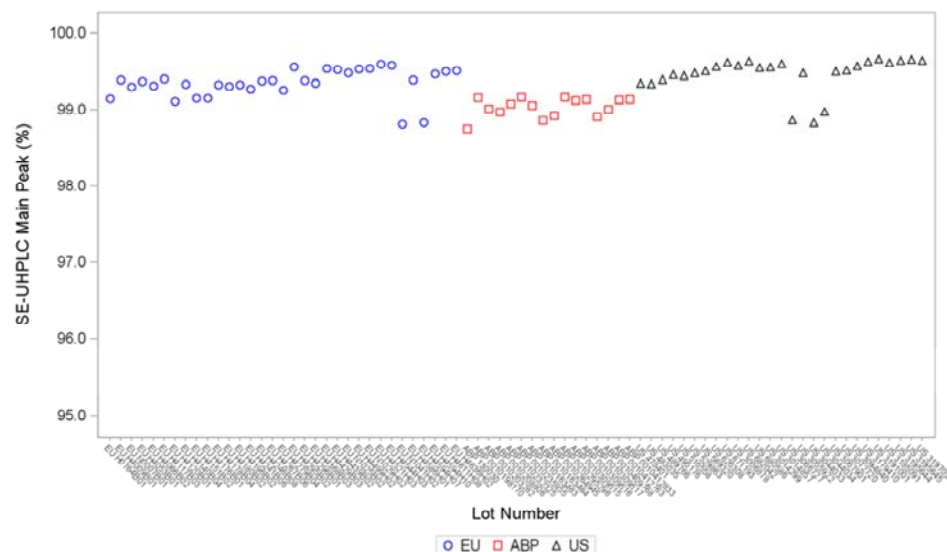


Figure 91. SE-UHPLC Main Peak Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US) First Time Point Analysis



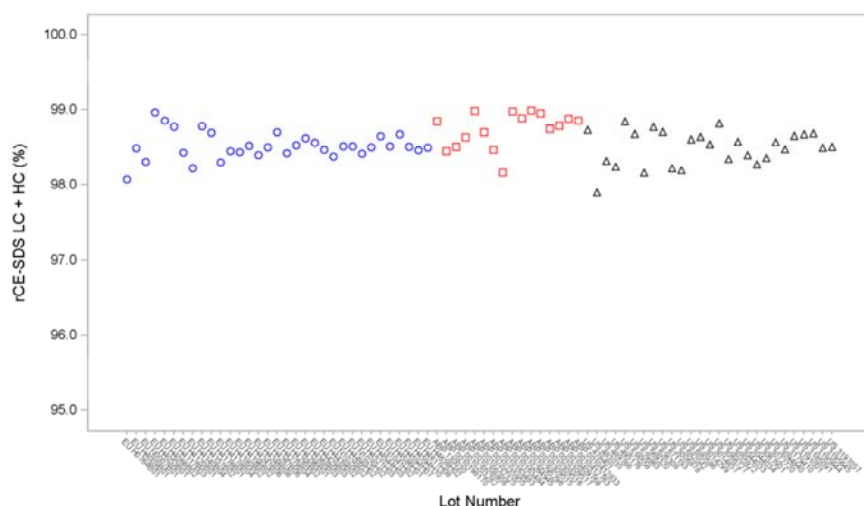
Reviewer Comment: As discussed in the original review cycle, the linear regression analysis for product age adjustments has the potential to introduce additional variables. Therefore, the age-adjusted results are only considered as supportive data for evaluation of stability-indicating attributes. The non-age-adjusted results together with the age-adjusted results suggest that the ABP 980 lots might have slightly lower levels of main peak and higher levels of HMW as compared to US-licensed Herceptin and EU-approved Herceptin, which is consistent as observed in the original BLA review cycle. The HMW species are predominantly dimers and the overall levels are low. Furthermore, biological characterization data support that these HMW species retain in vitro biological activity. Therefore, the observed differences in HMW and main peak do not preclude demonstration that ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin.

rCE-SDS (% HC+LC, % LMW + MMW, % NGHC)

The rCE-SDS results of three products are presented in Table 18 to Table 20. The quality range tests based on non-age-adjusted results showed that:

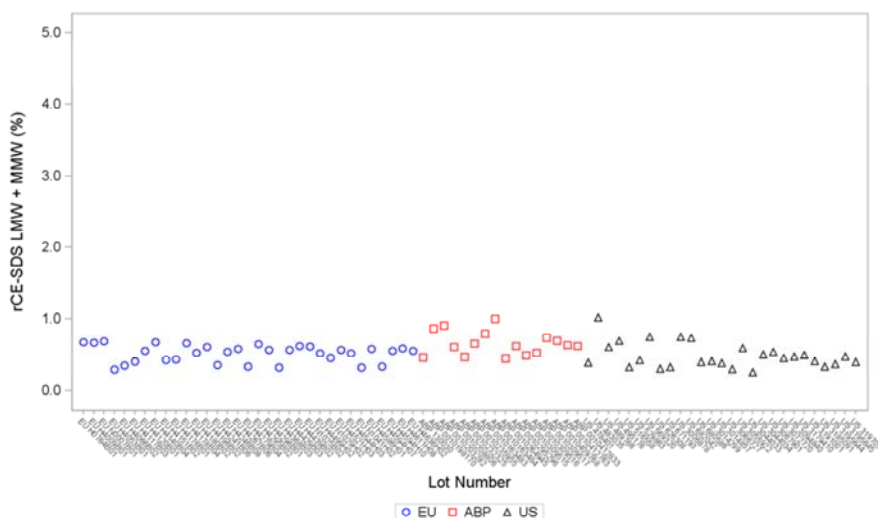
- 1) all ABP 980 lots fell within the US-licensed Herceptin quality range of %HC+LC and %LMW+MMW respectively, and none of the ABP 980 lots fell within the US-licensed Herceptin quality range of %NGHC;
- 2) all ABP 980 lots fell within the EU-approved Herceptin quality range of %HC+LC, 88% (14 of 16) of the ABP 980 lots fell within the EU-approved Herceptin quality range of %LMW+MMW, and 1 of the 16 ABP 980 lots fell within the EU-approved Herceptin quality range of NGHC;
- 3) all EU-approved Herceptin lots fell within the US-licensed Herceptin quality ranges of %HC+LC, %LMW + MMW, %NGHC.

Figure 18. rCE-SDS Purity (HC + LC) Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



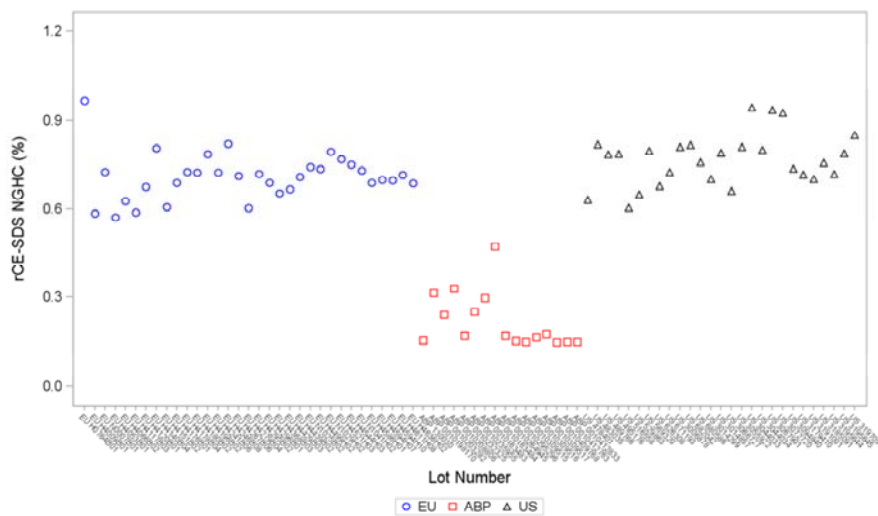
The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 19. rCE-SDS LMW + MMW Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 20. rCE-SDS NGHC Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Reviewer Comment: ABP 980 lots are similar to US-licensed Herceptin and EU-approved Herceptin in terms of %HC+LC. Regarding %HMW+MMW, although 2 ABP 980 lots fall out of the quality range of EU-approved Herceptin, the differences observed are within 0.1% of the quality range. The small differences do not preclude the determination of similarity of %HMW+MMW between ABP 980 and EU-approved Herceptin. Therefore, ABP 980 lots are similar to US-licensed Herceptin and EU-approved Herceptin in terms of %HMW+MMW. Regarding %NGHC, lower levels of NGHC are observed in ABP 980 lots as compared to US-licensed Herceptin and EU-approved Herceptin. The overall levels of NGHC are less than 1% and the minor quantitative differences observed are not expected to impact product biological activity. No new differences are observed as compared to data submitted during original review cycle. Furthermore, the FcγRIIIa binding are similar among three products. Therefore, the NGHC difference observed do not preclude the determination of similarity between ABP 980 and

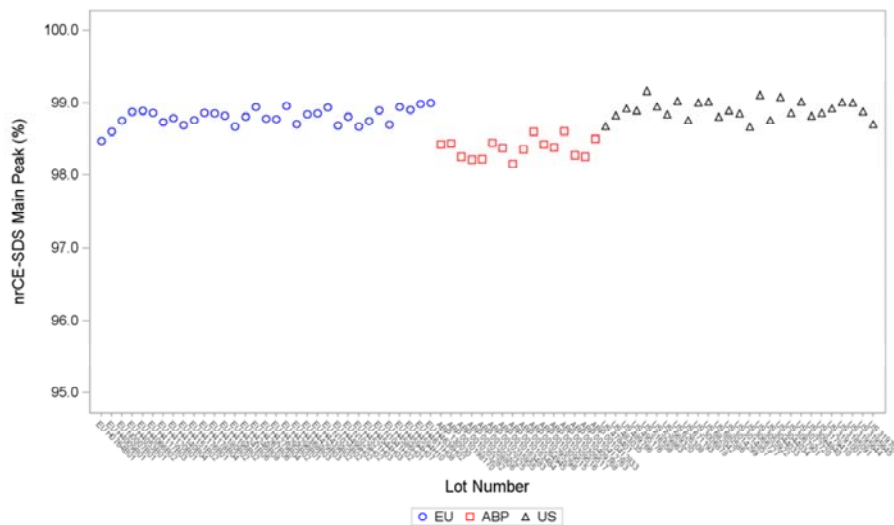
US-licensed Herceptin as well as EU-approved Herceptin. EU-approved Herceptin are similar with US-licensed Herceptin in terms of % HC+LC, % LMW + MMW, and % NGHC. In summary, the rCE-SDS data support the similarity between ABP 980 and US-licensed Herceptin, between ABP 980 and EU-approved Herceptin, between EU-approved Herceptin and US-licensed Herceptin.

nrCE-SDS (% main peak, % pre-peaks)

The nrCE-SDS results of the three products are presented in Figure 34 and Figure 35. The quality range tests based on non-age-adjusted results showed that:

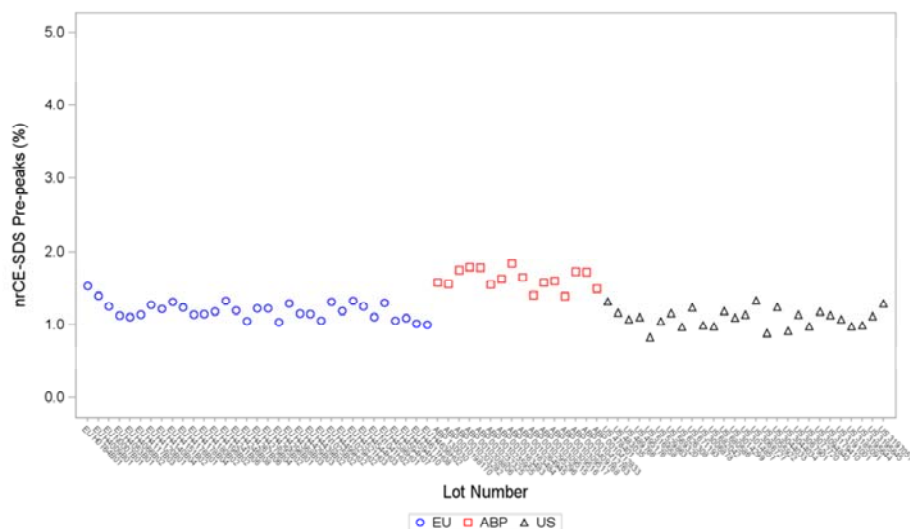
- 1) 2 of the 16 (13%) ABP 980 lots fell within the US-licensed Herceptin quality range of main peak, and 2 of the 16 (13%) ABP 980 lots fell within the US-licensed Herceptin quality range of pre-peaks;
- 2) 4 of the 16 (25%) ABP 980 lots fell within the EU-approved Herceptin quality range of main peak, 4 of the 16 (25%) ABP 980 lots fell within the EU-approved Herceptin quality range of pre-peaks;
- 3) 32 of the 33 (97%) EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of main peak, and 32 of the 33 (97%) EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of pre-peaks.

Figure 34. **nrCE-SDS Main Peak** Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 35. **nrCE-SDS Pre-peak** Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Reviewer Comment: The pre-peaks represent partially-reduced species with open disulfide structures and clipped species. A higher level of pre-peaks and corresponding lower level of main peak are observed for ABP 980 as compared to US-licensed Herceptin and EU-approved Herceptin, which was also observed during the first review cycle. The differences are minor and biological activity similarity assessment support similar biological activity of the three products. Furthermore, published literature support re-oxidation of antibody disulfide bonds in vivo. Therefore, the observed differences do not preclude the determination of similarity of ABP 980 to US-licensed Herceptin and EU-approved Herceptin. EU-approved Herceptin is similar to US-licensed Herceptin in terms of %main peak and %pre-peaks as demonstrated by the quality range test results.

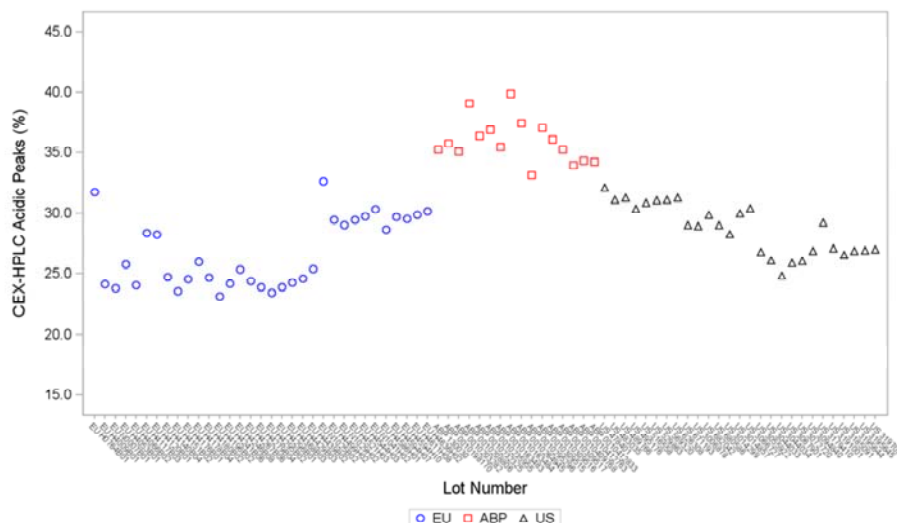
CEX-HPLC (% acidic peaks, % main peak, % basic peaks)

The CEX-HPLC results of three products are presented in Figure 47 (acidic peaks), Figure 98 (main peak), and Figure 99 (basic peaks). The quality range tests based on non-age-adjusted results showed that:

- 1) 4 of the 16 ABP 980 lots (25%) fell within the US-licensed Herceptin quality range of acidic peaks, 9 of the 16 ABP 980 lots (56%) fell within the US-licensed Herceptin quality range of main peak, and 14 of the 16 ABP 980 lots (88%) fell within the US-licensed Herceptin quality range of basic peaks;
- 2) 7 of the 16 ABP 980 lots (44%) fell within the EU-approved Herceptin quality range of acidic peaks, 11 of the 16 ABP 980 lots (69%) fell within the EU-approved Herceptin quality range of main peak, and 9 of the 16 ABP 980 lots (56%) fell within the EU-approved Herceptin quality range of basic peaks;

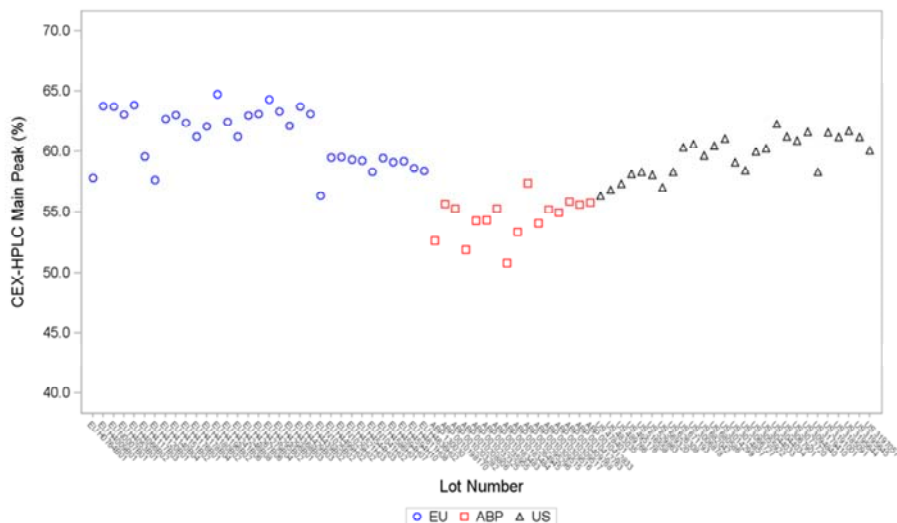
- 3) all the EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of acidic peaks, 32 of the 33 EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of main peak, and all the EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of basic peaks.

Figure 47. CEX- HPLC **Acidic Peaks** Non-age-adjusted Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



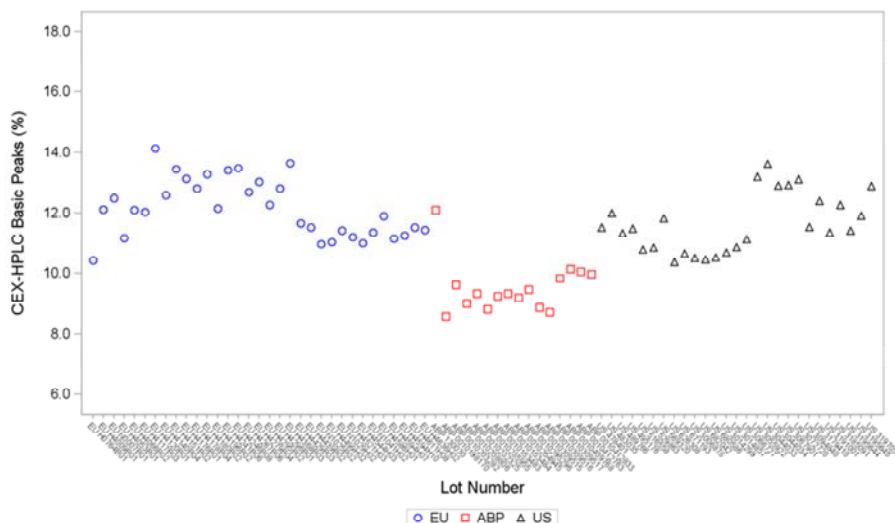
The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 98. CEX- HPLC **Main Peak** Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US) First Time Point Analysis



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 99. CEX- HPLC Basic Peaks Results for Trastuzumab (EU), ABP 980 and Trastuzumab (US) First Time Point Analysis



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Changes in CEX-HPLC main peak and basic peaks were observed over time at the recommended storage condition. Therefore, the quality range tests were performed on age-adjusted results as well. The quality range tests based on age-adjusted results showed that:

- 1) 3 of the 16 ABP 980 lots (19%) fell within the US-licensed Herceptin quality range of main peak, and all the ABP 980 lots fell within the US-licensed Herceptin quality range of basic peaks;
- 2) 9 of the 16 ABP 980 lots (56%) fell within the EU-approved Herceptin quality range of main peak, and all the ABP 980 lots fell within the EU-approved Herceptin quality range of basic peaks;
- 3) 29 of the 33 (88%) EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of main peak, and 32 of the 33 (97%) of the EU-approved Herceptin lots fell within the US-licensed Herceptin quality range of basic peaks.

Reviewer Comment: The ABP 980 lots show relatively lower levels of main peak and higher levels of acidic peaks as compared to US-licensed Herceptin and EU-approved Herceptin. This observation complies with those observed during the first review cycle. As discussed in the original BLA review, characterization data of each charge species (acidic, main, basic) show that acidic peaks contain deamidation at LC Asn30 and HC Asn55, non-consensus glycosylation, glycation, and fragments. Characterization data also demonstrate that the three products contain similar distributions of post-translational modifications. Additionally, corresponding fractions have similar biological activity among the three products. Furthermore, similar FcRn binding and functional activity results are observed between the three products. Therefore, the differences observed do not preclude determination of similarity of ABP 980 as compared to US-licensed Herceptin and EU-approved Herceptin. EU-approved Herceptin is similar to US-

licensed Herceptin with respect to CEX-HPLC aside from minor differences observed in the main peak level.

General Properties

Product Strength – Protein Content and Reconstituted Protein Concentration

For protein content assay (tier 3), ABP 980 420 mg presentation was compared with the US-licensed Herceptin 420 mg presentation and the ABP 980 150 mg presentation was compared with the EU-approved Herceptin presentation. The reconstituted protein concentration (tier 2) was compared across the different presentations and across all three products. For reconstitution, 7.2 mL of WFI was used for the 150 mg presentations (ABP 980 and EU-approved Herceptin) and 20 mL of WFI was used for the 420 mg presentations (ABP 980 and US-licensed Herceptin). The US-licensed Herceptin 150 mg presentation was reconstituted with 7.4 mL of WFI. Information of lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	32	27	30	The 3 ABP 980 ADL DP lots (420 mg) were included in the protein content and reconstituted protein concentration assays, the 6 US-licensed Herceptin 150 mg presentation lots were included in the reconstituted protein concentration assays of ASA update.
ASA in original BLA submission	29	21	30	

The protein content results of ABP 980 420 mg presentation lots were within similar ranges of US-licensed Herceptin 420 mg presentation lots (Figure 2). Similarly, the protein content results of ABP 980 150 mg presentation lots were within similar ranges of EU-approved Herceptin lots (Figure 3).

Figure 2. Protein Content Results for ABP 980 and Trastuzumab (US) for 420 mg Presentation

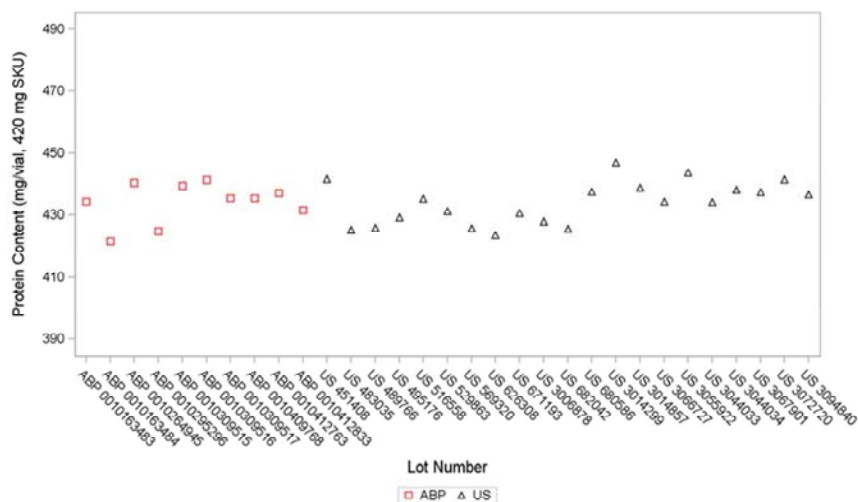
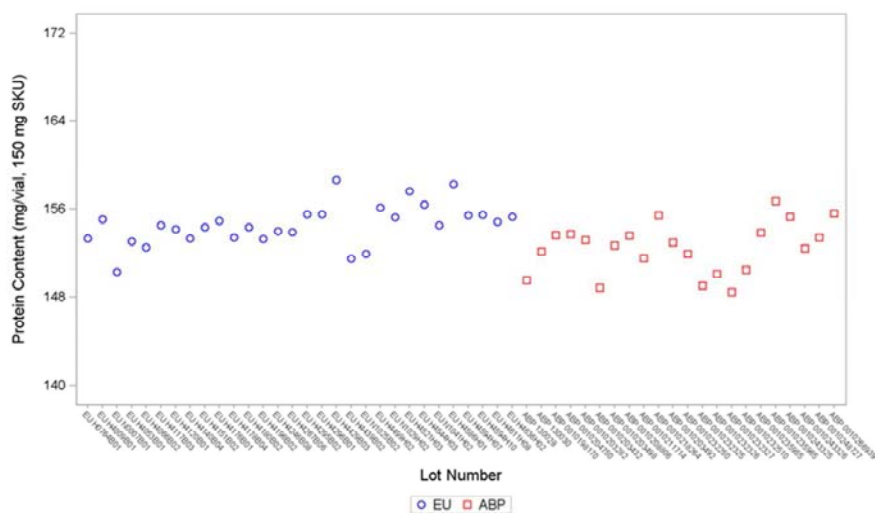
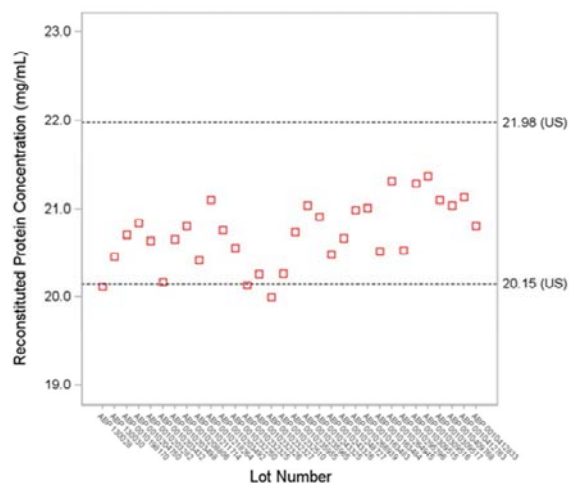


Figure 3. Protein Content Results for Trastuzumab (EU) and ABP 980 for 150 mg Presentation



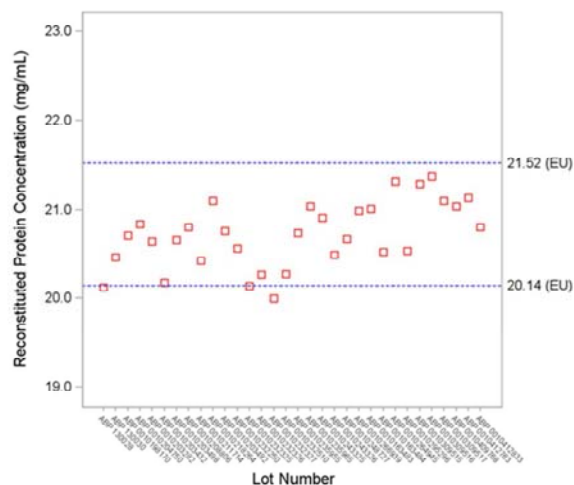
Regarding reconstituted protein concentration, 29 out of 32 (91%) of the ABP 980 lots were within the US-licensed Herceptin quality range (Figure 4), and 29 of 32 (91%) of the ABP 980 lots were within the EU-approved Herceptin quality range (Figure 5). All EU-approved Herceptin lots were within the US-licensed Herceptin quality range.

Figure 4. Reconstituted Protein Concentration – ABP 980 Compared to Trastuzumab (US) Quality Range



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Figure 5. Reconstituted Protein Concentration – ABP 980 Compared to Trastuzumab (EU) Quality Range



The last 3 ABP lots were manufactured at Amgen Technology Ireland Unlimited Company (ADL)

Reviewer Comment: The protein content and reconstituted protein concentration data support a determination of similarity between ABP 980 and US-licensed Herceptin, between ABP 980 and EU-approved Herceptin, and between EU-approved Herceptin and US-licensed Herceptin.

Reconstitution Time

Reconstitution time was classified as a tier 3 assay. The lot information used for reconstitution time assay is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	33	3	3	The 3 ABP 980 ADL DP lots were included in the reconstitution time assay of ASA update.
ASA in original BLA submission	30	3	3	

All lots tested completely dissolved within 5 minutes, which were consistent with the US-licensed Herceptin and EU-approved Herceptin labels.

Reviewer Comment: The reconstitution time data provided support a determination of similarity between ABP 980 and US-licensed Herceptin, between ABP 980 and EU-approved Herceptin, and between EU-approved Herceptin and US-licensed Herceptin.

Process-related Impurities

The Host Cell Protein (by ELISA), Protein A (by ELISA) and residual DNA (by qPCR) assays were updated using the 5 ABP 980 ARI DS lots. All three assays were classified as tier 3 assays. Information of lots used is summarized in the following table:

Analytical Similarity Assessment (ASA)	Number of lots used			Note
	ABP 980	US-licensed Herceptin	EU-approved Herceptin	
ASA update in BLA resubmission	27	3	3	The 5 ABP 980 ARI DS lots were included in the Host Cell Protein (ELISA), Protein A (ELISA) and residual DNA (qPCR) assays of ASA update.
ASA in original BLA submission	22	3	3	

For Host Cell Protein assay (ELISA), the ABP 980 lots showed slightly higher HCP levels compared to US-licensed Herceptin and EU-approved Herceptin lots. However, the overall HCP levels in ABP 980 lots samples were low ((b) (4) ng/mg). For protein A levels, results from all three products were < 1 ng/mg. For residual DNA, results from all three products were < 0.2 pg/mg.

Reviewer Comment: The HCP ELISA results are not unexpected since the HCP ELISA method used are optimized to detect HCP in ABP 980. The HCP ELISA, Protein A ELISA, and residual DNA assay results support a determination of similarity between ABP 980 and US-licensed Herceptin, between ABP 980 and EU-approved Herceptin, between EU-approved Herceptin and US-licensed Herceptin.



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of review:	May 23, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Lei Zhang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research II
Application:	BLA 761073
Applicant:	Amgen Inc
Submission Date:	December 28, 2018
Product:	Kanjinti (trastuzumab-anns)
Dosage form(s):	For injection
Strength and Container-Closure:	420 mg/vial multiple-dose vial
Purpose of review:	The Applicant submitted a biologics license application for Agency review.
Recommendations:	The prescribing information (submitted on May 10, 2019), container labels (submitted on April 15, 2019), and carton labeling (submitted on May 22, 2019) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this review

DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

CONCLUSION

The prescribing information (submitted on May 10, 2019), container labels (submitted on April 15, 2019), and carton labeling (submitted on May 22, 2019) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on March 8, 2019

<\\cdsesub1\evsprod\bla761073\0042\m1\us\uspi-redline.docx>)

Container Labels (submitted on December 28, 2018)

(b) (4)



Vicky
Borders-Hemphill

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Lei
Zhang

Digitally signed by Lei Zhang
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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761073/0**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting QAL, DMA Branch IV
Subject: Review of 351(k) BLA Resubmission
Applicant: Amgen, Inc.
US License: 1080
Product: KANJINTI (ABP 980; proposed biosimilar to trastuzumab)
Indication: Breast Cancer
Dosage: Lyophilized powder for IV infusion, 420 mg/vial
DS Facilities: Immunex Rhode Island Corporation (FEI: 3003359885)

(b) (4)

Receipt Date: 12/28/2018

Action Date: 6/28/2019

Recommendation for Approvability: STN 761073 was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Summary

Amgen Inc. submitted 351(k) BLA 761073 in eCTD format on 28 July 2017 to license the manufacture of ABP 980, a proposed biosimilar to Herceptin®. A Complete Response Letter (CRL) was subsequently provided to the applicant 25 May 2018. This resubmission was submitted on 28 Dec 2018 to address the deficiencies listed in the CRL.

There were no items in the CRL pertaining to product quality microbiology for the DS portion of the BLA, based on DS manufacturing at (b) (4) as described in the 9 April 2018 review by Kathleen Jones, Ph.D. However, Immunex Rhode Island Corporation (also referred to as Amgen Rhode Island or ARI) was added as an additional drug substance manufacturing site in this resubmission. This review contains the assessment of the drug substance portion of the BLA resubmission from a product quality microbiology perspective.

For review of the Drug Product (DP) portion of the resubmission from a sterility assurance perspective, see the assessment by Jessica Hankins, Ph.D.

Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0037	12/28/2018	BLA Resubmission
eCTD 0044	4/10/2019	Response to information request

Product Quality Microbiology Assessment

3.2.S DRUG SUBSTANCE

(b) (4)

SATISFACTORY

Conclusion

- I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.
- III. Refer to Panorama for cGMP status of the relevant facilities.

Microbiology Information Request dated 10 April 2019

DRUG SUBSTANCE

Section 3.2.S.2.5 – *Process Validation and/or Evaluation*

(b) (4)



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

Date: 05/24/2018
To: Administrative File, STN 761073/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao (Peter) Qiu, Ph.D., Supervisory Consumer Safety Officer
CDER/OPQ/OPF/DIA, Branch 1 Chief
Subject: New Biologic License Application (BLA)
US License: 1080
Applicant: Amgen Inc.
Mfg Facility: Drug Substance: (b) (4) for ABP 980 DS
Drug Product: (b) (4)
Product: KANJINTI (trastuzumab-atzu)
Dosage: Lyophilized powder, 420 mg, Intravenous infusion
Indication: For adjuvant breast cancer, metastatic breast cancer, and metastatic gastric cancer.
Due Date: May 28, 2018

Facilities Assessment: Addendum to the original facilities assessment dated 05/22/2018, with final approval 05/23/2018.

SUMMARY

The facilities assessment dated 05/22/2018 with final approval 05/23/2018 stated the following for Reviewer Comment 12:

Reviewer Comment 12: *The proposed facilities for manufacture and testing for ABP 980 DP and bWFI are currently in a state of compliance and are acceptable from a facilities assessment standpoint.*

For this addendum, Reviewer Comment 12 has been corrected to accurately state the compliance status of facilities:

Amended Reviewer Comment 12: *The (b) (4) facility proposed for ABP 980 DP (b) (4) manufacture and testing has an unacceptable compliance status based on the (b) (4) inspection and has a withhold recommendation. All other facilities proposed for testing and packaging are currently in a state of compliance.*

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

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

Wayne E.
Seifert -S

Digitally signed by Wayne E. Seifert -S
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ou=HHS, ou=FDA, ou=People,
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Date: 2018.05.24 16:36:30 -04'00'

Zhihao
Qiu -S

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DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Zhihao Qiu -S,
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0438274
Date: 2018.05.24 16:41:31 -04'00'

BLA 761073

KANJINTI (trastuzumab-anns)

Amgen, Inc.

OBP CMC Review Data Sheet

1. **BLA#:** 761073/0

2. **Review Date:** March 8, 2018

3. Primary Review Team:

a. Medical Officer:	Lynn Howie Jennifer Gao Laleh Amiri Kordestani (Team Leader, CDTL)
b. Pharm/Tox:	Kimberly Ringgold Todd Palmby
c. Product Quality Team:	Chen Sun (Drug Substance, Analytical Similarity) Chih-Jung Hsu (Drug Product, Immunogenicity Assays) Patrick Lynch (Team Leader, ATL) Howard Anderson (Review Chief) Kathleen Jones (Microbiology Drug Substance) Jessica Hankins (Microbiology Drug Product) Maria Candau-Chacon (QAL)
d. Facilities:	Wayne Seifert Zhihao Peter Qiu
e. Clinical Pharmacology:	Olanrewaju Okusanya Sarah Schrieber
f. Statistics:	Joyce Cheng (Biostatistics) Yu-Yi Hsu (CMC Statistics) Meiyu Shen (CMC Statistics, Lead)
g. OBP Labeling:	Vicky Borders-Hemphill
h. RBPM:	Keith Olin
i. RPM:	Amy Tilley

4. Major GRMP Deadlines:

a. Filing Meeting:	August 11, 2017
b. Mid-cycle meeting:	December 12, 2017
c. Wrap-up meeting:	April 9, 2018
d. Primary review due:	April 19, 2018
e. Secondary review due:	April 28, 2018
f. PDUFA action date:	May 28, 2018

5. Communications with Sponsor:

Communication/Document:	Date:
Information Request #1	October 25, 2017
Information Request #2	December 1, 2017
Information Request #3	January 17, 2018
Information Request #4	February 8, 2018
Information Request #5	February 20, 2018
Information Request #6	March 8, 2018
Information Request #7	March 19, 2018

Information Request #8	March 28, 2018
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6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761073/12 (Response to IR #1)	November 03, 2017	Yes
STN 761073/15 (Response to IR #2)	December 8, 2017	Yes
STN 761073/19 (Response to IR #3)	January 24, 2018	Yes
STN 761073/23 (Response to IR #4)	February 26, 2018	Yes
STN 761073/24 (Response to IR #5)	March 5, 2018	Yes
STN 761073/26 (Response to IR #6)	March 16, 2018	Yes
STN 761073/29 (Response to IR #7)	March 26, 2018	Yes
STN 761073/31 (Response to IR #8)	April 4, 2018	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Kanjinti
- b. Trade Name: Kanjinti
- c. Non-Proprietary Name/USAN: Trastuzumab-anns
- d. CAS Name: 1446410-98-5
- e. Common Name: ABP 980
- f. INN Name: Trastuzumab
- g. Compendial Name: Not Applicable
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P04626 (ERBB2_HUMAN) [ABP 980]
- i. Other names: Not Applicable

8. Pharmacological Category: Therapeutic recombinant humanized monoclonal IgG1 antibody to HER2

9. Dosage Form: For injection

10. Strength/Potency:

- (i): The concentration/strength of the Drug Product: 420 mg
- (ii): Type of potency assay(s): Cell based proliferation inhibition bioassay

11. Route of Administration: Intravenous (IV) infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	No further reviews were performed. From the OBP perspective, adequate information is provided in the application.
			Yes	
			Yes	
			Yes	

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

13. Inspectional Activities:

A pre-licensure inspection (PLI) was conducted from (b) (4) at the following facility:

(b) (4)

The PLI covered the manufacturing operations for ABP 980 DS under BLA STN 761073 and was conducted by reviewers from OBP (Patrick Lynch and Chen Sun), DIA (Wayne Seifert), and DMA (Kathleen Jones and Maria Jose Lopez-Barragan). The PLI covered quality assessment procedures, manufacturing process, facilities and equipment, material management, data entry, contamination prevention, laboratory controls, and training programs. Assessment was made in accordance with ICH Q7A. A ten items 483 was issued with respect to deviation procedures, laboratory controls, written procedures, cleaning validation, materials management, document review, training review, equipment performance qualification, facility qualification, and monitoring of utilities.

14. Consults Requested by OBP: None

15. Quality by Design Elements:

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

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

16. Precedents: None

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation:

The data submitted in BLA 761073 support the conclusion that the manufacturing process of Kanjinti (trastuzumab-anns) is well controlled and leads to a product that is pure and potent. With respect to analytical similarity, Kanjinti appears to be highly similar to US-licensed Herceptin. From the product quality perspective, I recommend Kanjinti (trastuzumab) be approved for human use under conditions specified in the package insert.

The original OBP CMC review was submitted and signed in the CDER Informatics Platform on April 11, 2018 with a recommendation for approval. At the request of the Office of Chief Counsel (OCC), the

review was subsequently revised and resubmitted to the CDER Informatics Platform on May 21, 2018. This review reflects the revised final OBP CMC review and recommendation of approval.

II. List of Deficiencies to be Communicated:

Not applicable

III. List of Post-Marketing Commitments/Requirements:

The following is a draft post-marketing commitment.

(b) (4)

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c). This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This waiver is appropriate and found acceptable.

V. Primary Container Labeling Review:

The primary and secondary container closure labeling review is performed in a separate review by Vicky Borders-Hemphill.

VI. Review of Common Technical Document- Quality Module 3.2: Refer below

VII. Review of Immunogenicity Assays- Module 5.3.1.4: Refer below. Review of the immunogenicity assays is performed by Chih-Jung Hsu.

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APPEARS THIS WAY ON ORIGINAL

Description of Drug Substance and Drug Product

S. Drug Substance

3.2.S.1.2 Structure

ABP 980 is a full-length humanized monoclonal IgG1, which has been developed as a biosimilar to US-licensed Herceptin (trastuzumab). Each light chain (κ) contains 214 amino acid residues with 2 intramolecular disulfide bonds, and each heavy chain contains 449 amino acid residues with 4 intramolecular disulfide bonds. ABP 980 contains 32 total cysteine residues involved in 16 intrachain or interchain disulfide bonds. Each heavy chain contains an N-linked glycan at ASN 300. The expected amino acid sequences of the heavy and light chain components are listed in the figures below.

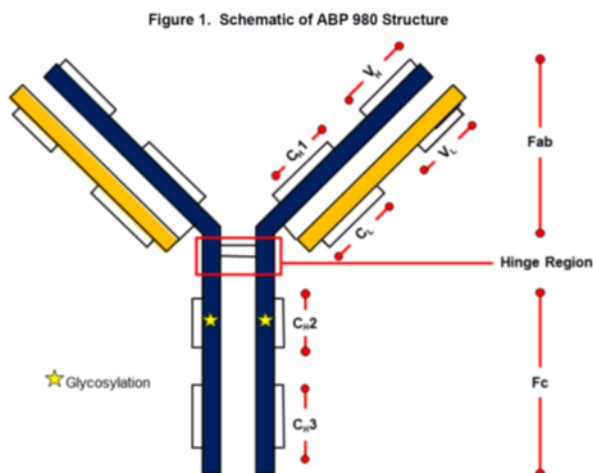


Figure 4. Nucleotide and Amino Acid Sequences of the DNA for ABP 980 HC

```

M D M R A P A Q I F G F L L L L F P G T
1 ATGGACATGAGGGCCCCAGGCCAGATTTTCGGCTTCTGCTGCTGTTCCCCGGCACC
R S E V Q L V E S G G G L V Q P G G S L
61 AGATCTGAGGTGACGTGGTGCAGAGCGGCGAGGGCTGGTGCAGCCAGGCGGAGCGCTG
R L S C A A S G F N I K D T Y I H W V R
121 AGGCTGCTCTGCGCCGCCAGCGGCTTCAACATCAAGGACACCTACATCCACTGGGTGCGG
Q A P G K G L E W V A R I Y P T N G Y T
181 CAGGCCCGAGGCAAGGGCTGGAGTGGTGGCCAGGATCTACCCCAACGAGCTACACC
R Y A D S V K G R F T I S A D T S K N T
241 AGATACGCCGACAGCGTGAAGGGCAGGTTCAACATCAGCGCCGACACGACGAAGAACAC
A Y L Q M N S L R A E D T A V Y Y C S R
301 GCCTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGACTACTGCAGCAGA
W G G D G F Y A M D Y W G Q G T L V T V
361 TGGGGCGGGGACGGCTTCTACGCTATGGACTACTGGGCGGAGGACCCCTGGTGCAGCGTG
S S A S T K G P S V F P L A P S S K S T
421 AGCAGCGCCAGCAGCAAGGGCCCTCCGTTCCCGCTGGGCCCCAGCAGCAAGAGCACC
S G G T A A L G C L V K D Y F P E P V T
481 AGCGGCGGACAGCCGCCCTGGGCTGCTGGTGAAGGACTACTTCCCGAGCCCGTGACC
V S W N S G A L T S G V H T F P A V L Q
541 GTGTCTGGAACAGCGGAGCCCTGACCTCCGCGGTGCACACCTTCCCGCCGTGCTGCAG
S S G L Y S L S S V V T V P S S S L G T
601 AGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGAAGTCCCGCAGCAGCAGCCTGGGCACC
Q T Y I C H V N H K P S N T K V D K K V
661 CAGACCTACATCTGCAACGTGAACCAAGCCAGCAACCAAGGTGGACAGAGAGGTG
E P K S C D K T H T C P P C P A P E L L
721 GAGCCCAAGAGCTGCGACAAGACCAACCTGCCCCCTGCCCCAGCCCAAGAGCTGCTG
G G P S V F L F P P K P K D T L M I S R
781 GGGGACCCAGCGTGTCTCTGTTCCCCCAAGCCCAAGGACACCTGATGATCAGCAGG
T P E V T C V V V D V S H E D P E V K F
841 ACCCCGAGGTGACCTGCGTGGTGGTGGAGCTGAGCCAGAGGACCCAGAGGTGAAGTTC
N W Y V D G V E V H N A K T K P R E E Q
901 AACTGTACGTGGACGGCGTGGAGGTGCACAAGCCCAAGCCCAAGAGGAGGAGCAG
Y N S T Y R V V S V L T V L H Q D W L N
961 TACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGTGACACGAGCTGGCTGAAC
G K E Y K C K V S N K A L P A P I E K T
1021 GGCAGGAATACAAGTGCAGGCTCTCAACAGGGCCCTGCCAGCCCCATCGAGAAAACC
I S K A K G Q P R E P Q V Y T L P P S R
1081 ATCAGCAAGGCCAGGGCCAGCCAGGAGCCCGAGGTGTACACCTGCCCGCCAGCGCG
E E M T K N Q V S L T C L V K G F Y P S
1141 GAGGAGATGACCAAGAACAGGTGTCTGCTGCTGGTGAAGGGCTTACCCACAGC
D I A V E W E S N G Q P E N N Y K T T P
1201 GACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGGACAACTACAAGACCAACCC
P V L D S D G S F F L Y S K L T V D K S
1261 CCAGTGTGAGCAGCGAGCGGAGCTTCTCTGTACAGCAAGCTGACCTGGACAGAGGC
R W Q Q G N V F S C S V M H E A L H N H
1321 AGGTGGCAGCAGGGCAAGCTGTTCAGCTGAGCGTGATGCAGAGGCCCTGCACAAACC
Y T Q K S L S L S P G
1381 TACACCCAGAGAGCTGTCTGAGCCCGGC

```

Nucleotides 1 to 66 encode the signal peptide. The first amino acid of the mature heavy chain (E, corresponding to nucleotides 67 to 69) is indicated in bold and enlarged text.

Figure 5. Nucleotide and Amino Acid Sequences of the DNA for ABP 980 LC

```

M D M R A P A Q I F G F L L L L F P G T
1 ATGGACATGAGGGCCCCAGGCCAGATTTTCGGCTTCTGCTGCTGTTCCCCGGCACC
R S D I Q M T Q S P S S L S A S V G D R
61 AGATCTGACATCCAGATGACCCAGAGCCCGAGCAGCTGAGCGCCAGCGTGGGCGACAGG
V T I T C R A S Q D V N T A V A W Y Q Q
121 GTGACCATCACCTGCAGGGCCAGCCAGGAGTGAACACCGCGTGGCTGGTATCAGCAG
K P G K A P K L L I Y S A S F L Y S G V
181 AAGCCCGGCAAGGCCCAAGCTGCTGATCTACAGCGCAGCTTCTGTACAGCGCGGTG
P S R F S G S R S G T D F T L T I S S L
241 CCCAGCAGTTTACGGCAGCAGGTCGGCAGCGACTTCACTGACCATCAGCAGCCTG
Q P E D F A T Y Y C Q Q H Y T T P P T F
301 CAGCCCGAGGACTTCGCCACTACTACTGCCAGCAGCACTACCAACCCCCCACCTTC
G Q G T K V E I K R T V A A P S V F I F
361 GGCAGGGCACCAGGTGGAGATCAAGAGGACCGTGGCGCTCCAGCGTGTTCATCTTC
P P S D E Q L K S G T A S V V C L L N N
421 CCCCCAGGACGAGCAGCTGAAGAGCGGACCGCTCGTGGTGTGCTGCTGAACAAC
F Y P R E A K V Q W K V D N A L Q S G N
481 TTCTACCCCGGGAGGCCAAGGTGAGTGGAGGTGGACACGCCCTGCAGAGCGGCAAC
S Q E S V T E Q D S K D S T Y S L S S T
541 AGCCAGGAGCGTCAACGAGCAGGACAGGAGCTCACTACAGCCTGAGCAGCACC
L T L S K A D Y E K H K V Y A C E V T H
601 CTGACCTGAGCAGGCGGACTACGAGAAGCAAGGTGTACGCTGCGAGGTGACCCAC
Q G L S S P V T K S F N R G E C
661 CAGGGCTGTCCAGCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC

```

Nucleotides 1 to 66 encode the signal peptide. The first amino acid of the mature light chain (D, corresponding to nucleotides 67 to 69) is indicated in bold and enlarged text.

3.2.S.1.3 General Properties

Molecular mass: 145,222 (experimental), 148,219 (theoretical with predominant glycan)

Isoelectric point (pI): 8.8

Melting point: 70.9°C for C_H2, 82.6°C for Fab and C_H3

Extinction coefficient: 1.5 mg⁻¹ cm⁻¹ mL at A280 nm

The HER2 (or c erbB2) proto oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. ABP 980 specifically binds to the extracellular domain (ECD) of HER2. Binding to HER2 that is expressed at high levels on the surface of tumor cells results in inhibition of the ligand-independent HER2 signaling pathway; subsequently, inhibiting cell proliferation. Additionally, ABP 980 also binds to the FcγRIIIa receptor and mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The testing and manufacture for nivolumab is performed at the following facilities (tables reproduced directly from the submission).

Table 1. Drug Substance Facility Responsibilities

Facility	Address	Responsibility	FDA Registration Number
(b) (4)	(b) (4)	Drug substance manufacture Drug substance in-process and lot release testing	(b) (4)
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320 USA	Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank storage Manufacture of working cell banks	FEI: 2026154 DUNS: 039976196
Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road, Dun Laoghaire, Co. Dublin, Ireland	Drug substance in-process, lot release and stability testing, and storage	FEI: 3002808497 DUNS: 896293920
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817 United States	Unprocessed bulk mycoplasma testing Drug substance in-process, lot release and stability testing	FEI: 3003359885 DUNS: 968084785
Amgen Manufacturing Limited (AML)	State Road 31, Km 24.6, Juncos, Puerto Rico 00777-4060 United States	Drug substance in-process, lot release, and stability testing	FEI: 1000110364 DUNS: 785800020

FEI= Facility Establishment Identifier

DUNS = Data Universal Numbering System

Table 2. Contract Testing Laboratories

Facility	Address	Type of Testing	FDA Registration Number
(b) (4)	(b) (4)	Unprocessed bulk mycoplasma and adventitious viral testing	(b) (4)
		Unprocessed bulk mycoplasma and adventitious viral testing	

FEI = Facility Establishment Identifier

DUNS = Data Universal Numbering System

Table 3. Sites Used for ABP 980 Drug Substance Release/Stability Testing

Test	(b) (4)	Testing Site			
		ATO	ARI	ADL	AML
Appearance	-	X	X	X	X
ABP 980 ELISA	-	X	-	X	-
CEX-HPLC	-	X	X	X	-
SE-UHPLC	-	X	X	X	-
Bacterial endotoxins	X	X	-	X	X
Bioburden	X	X	-	-	-
Proliferation inhibition bioassay	-	X	-	X	-
Protein concentration	X	X	-	X	X
pH	X	X	-	X	X
Polysorbate 20	-	X	X	X	-
Glycan map	-	X	-	-	-

ATO = Amgen Thousand Oaks; AML = Amgen Manufacturing Limited; ADL = Amgen Technology Ireland, ARI = Amgen Rhode Island
"X" in each cell indicates that the site has been qualified to perform this testing

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

(b) (4)

(b) (4)

3.2.R.4 Analytical Similarity and Analytical Bridge

The below sections on Analytical Similarity and the Analytical Bridge were written by Chen Sun.

EU-approved Herceptin was used as a comparator to ABP 980 in the clinical study in the patient population (Table 1).

Table 1. ABP 980 Clinical Studies to Support the BLA

Study Number	Subject Population	Type	Products
20130119	Healthy male subjects	PK similarity	ABP 980 Trasutuzmab (US) Trastuzumab (EU)
20120283	Subjects with HER2-positive early breast cancer	Efficacy, safety, and immunogenicity	ABP 980 Trastuzumab (EU)

EU = European Union; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic;
US = United States.

To support the use of clinical data generated using EU-approved Herceptin as a comparator, Amgen established a three-way PK bridge, and an analytical bridge between ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The following pair-wise comparisons were provided to support the analytical bridge.

- ABP 980 to US-licensed Herceptin
- ABP 980 to EU-approved Herceptin
- EU-approved Herceptin to US-licensed Herceptin

Reviewer Comment: The acceptability of the three-way pharmacokinetics study to support the use of EU-approved Herceptin as a comparator in clinical study 20120283 and demonstrate a pharmacokinetics bridge between ABP 980, EU-approved Herceptin, and US-licensed Herceptin are reviewed by the Office of Clinical Pharmacology. The similarity assessment is reviewed below.

Tables 1, 2, and 3 below present lots of ABP 980 used in the similarity assessment, including 150 mg and 420 mg presentations manufactured at (b) (4) scales (refer to section 3.2.S.2.6 and 3.2.P.2.3 regarding DS and DP comparability). The product lots for the similarity assessment were selected based on the following considerations:

- All ABP 980 DS lots used for manufacture of DP lots used in clinical studies are represented.
- For attributes influenced by the DS manufacturing process, a single DP lot for each independent DS lot is included. Data from DS lots are included in the similarity assessment in cases where an associated DP lot is not available.
- For attributes influenced by the DP manufacturing process, all available DP lots, including those from pooled DP lots, were included.
- For attributes which are expected to change over time at the recommended storage condition, the DP lots placed on stability are included.
- For process-related impurities, data from the DS lots are included in the similarity assessment.

Table 1. ABP 980 Lots Included in the Analytical Similarity Assessment (150 mg Presentation)

Drug Product Lot Number	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Drug Product Intended Use ^a	Drug Substance Lot Number ^b	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
130028	(b) (4)	Dec 2013	Clinical, nonclinical	0010200648	(b) (4)	Nov 2013	Clinical, nonclinical, stability
130029		Jan 2014	Development	0010195050		Dec 2013	Clinical, stability
130030		Mar 2014	Clinical	0010195050 1401-085		Dec 2013 Feb 2014	Clinical, stability Clinical
0010198170	ATO	Apr 2014	Clinical, stability	0010195050		Dec 2013	Clinical, stability
0010204750	ATO	May 2014	Clinical	0010195050		Dec 2013	Clinical, stability
0010203282	ATO	Aug 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010203432	ATO	Sep 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010203498	ATO	Oct 2014	Clinical	0010209656		May 2014	Clinical, primary reference standard, working reference standard
0010208806	ATO	Oct 2014	Clinical	0010220792		Aug 2014	Clinical
0010211714	(b) (4)	Nov 2014	Clinical	0010220792		Aug 2014	Clinical
0010218264	ATO	Nov 2014	Clinical	0010220792		Aug 2014	Clinical

Drug Product Lot Number	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Drug Product Intended Use ^a	Drug Substance Lot Number ^b	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010203492	ATO	Feb 2015	Clinical	0010229668	(b) (4)	Nov 2014	Clinical
0010232250	ATO	Mar 2015	Clinical	0010220792 0010229668		Aug 2014 Nov 2014	Clinical Clinical
0010232325	ATO	Mar 2015	Clinical	0010232685		Jan 2015	Clinical
0010232326	ATO	Apr 2015	Clinical	0010232685		Jan 2015	Clinical
0010232327	ATO	Apr 2015	Clinical	0010232685		Jan 2015	Clinical
0010232510	ATO	May 2015	Clinical	0010220792 0010232685		Aug 2014 Jan 2015	Clinical Clinical
0010235955	ATO	Jun 2015	Clinical	0010239533		May 2015	Clinical
0010235965	ATO	Jul 2015	Clinical	0010239533		May 2015	Clinical
0010243325	ATO	Jul 2015	Clinical	0010239533		May 2015	Clinical
0010243326	ATO	Aug 2015	Clinical	0010239533 0010247558		May 2015 May 2015	Clinical Clinical
0010248727	ATO	Aug 2015	Stability	0010247558		May 2015	Clinical
0010266939	ATO	Jan 2016	Stability	0010247558		May 2015	Clinical

Table 2. ABP 980 Lots Included in the Analytical Similarity Assessment (440 mg Presentation^c)

Drug Product Lot Number	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Drug Product Intended Use ^a	Drug Substance Lot Number ^b	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010163483	ATO	Apr 2014	Clinical, stability	0010200648	(b) (4)	Nov 2013	Clinical, nonclinical, stability
0010163484	ATO	Jan 2015	Stability	0010229668		Nov 2014	Clinical
0010264945	ATO	Jan 2016	Stability	0010247558		May 2015	Clinical
0010295296	ATO	Sep 2016	Development	0010292708		Feb 2016	Development, stability
0010309515	(b) (4)	Sep 2016	Process validation, Stability	0010253480		Jul 2015	Process validation
0010309516		Sep 2016	Process validation, Stability	0010262998		Dec 2015	Validation
0010309517		Sep 2016	Process validation, Stability	0010293548 0010294000 0010297878		May 2016 May 2016 Jun 2016	Process validation, stability Process validation, stability Process validation

Table 3. ABP 980 Lots Included in the Analytical Similarity Assessment (Drug Substance)

Drug Substance Lot Number ^b	Drug Substance Manufacturing Site	Drug Substance Manufacturing Scale	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010253477	(b) (4)	(b) (4)	Jun 2015	Process validation
0010253479			Jul 2015	Process validation
0010253481			Aug 2015	Process validation, stability
0010253482			Aug 2015	Validation
0010253484			Sep 2015	Validation, LIVCA
0010262996			Sep 2015	Validation
0010262997			Nov 2015	Validation
0010262999			Dec 2015	Validation
0010302656			Aug 2016	Process validation

LIVCA = limit of in vitro cell age study

Reviewer Comments: It is noted that a single DS lot might be used to produce multiple DP lots, while multiple DS lots can be combined to produce a single DP lot. However, a sufficient number of

independent lots from the commercial process were used in the similarity assessment. The selection of product lots for the similarity assessment appears acceptable.

In total, 23 lots of US-licensed Herceptin and 33 lots EU-approved Herceptin, including all lots used in the clinical studies, were used in the similarity assessment.

Reviewer Comment: *The selection of US-licensed and EU-approved Herceptin lots appear to be acceptable. These lots were selected across the product shelf-life, thus it is likely that the expected range of variability for these products is captured in the similarity testing.*

A tier-based system was used for the assessment of analytical data based on clinical relevance and mechanism of action. Quality attributes with the highest risk (Tier 1) were assessed by equivalency testing based on means or medians. Tier 2 includes attributes with moderate risk to clinical outcomes were evaluated using quality ranges (Mean $\pm$ 3xSD) established from US-licensed Herceptin lots and EU-approved Herceptin lots, respectively. For quality attributes with the low risk (Tier 3), a qualitative comparison of the data was performed.

Reviewer Comment: *The acceptability of the equivalency testing methods used to support similarity assessment of Tier 1 attributes is deferred to the CMC statistical reviewer.*

The samples of ABP 980, US-licensed Herceptin, and EU-approved Herceptin were assessed either by side-by-side testing, independent testing, or age-dependent testing based on the nature of the attribute assessed and method capability. For US-licensed Herceptin and EU-approved Herceptin lots included in the age-adjusted similarity assessment, the age at the time of testing was calculated according to the lot expiry date and presumed 48 month shelf life. For ABP 980 lots, the age of product was calculated based on the manufacturing date.

A summary of the similarity assessment is presented in the following table. Throughout the similarity assessment, the number of lots analyzed will be represented as ABP 980: US-licensed Herceptin: EU-approved Herceptin.

Reviewer Comments: *Method qualification/verification was considered for all methods used in the similarity assessment. For methods proposed for DS and DP specifications or included in the integrated control strategy, information regarding method qualification is presented section 3.2.S.4.3 and section 3.2.P.5.3. For general characterization tests (e.g., FTIR or peptide map) used for assessment of Tier 3 attributes, data provided in the submission was sufficient to allow meaningful evaluation of the results, and thus no product-specific method qualification was requested. Method qualification of certain functional assays, for which method capability could impact interpretation of the results, were requested in an IR dated October 25, 2017 and provided by Amgen on November 3, 2017.*

Several assays included a set of “age-adjusted” values for attributes known to change over the course of shelf life. In these experiments, the applicant extrapolated individual values to the proposed shelf life (ABP 980) and the presumed shelf life (US-licensed Herceptin and EU-Approved Herceptin) and used those estimates in the similarity assessment. This review considered both the non-extrapolated values

and the extrapolated ones. Less manipulated data (i.e., non age-adjusted) are generally preferred for use in the primary similarity evaluation because the age-adjustment introduces additional variable(s) to the analysis. However, the age-adjusted results were considered as supportive data for stability-indicating attributes potentially impacted by differences in lot age distributions. The non-extrapolated (i.e., non age-adjusted) values are reflected in the ranges presented in the table below.

Similarity assessment criteria established by Amgen were not met for several attribute comparisons. In each of these instances, differences are justified as minor and do not preclude a demonstration that ABP 980 is highly similar to US-Herceptin. Similarity assessments for individual attributes are reviewed in detail below in this section of the memo.

Reviewer Comments:

The results of the similarity assessment support the following conclusions:

- ABP 980 is highly similar to US-licensed Herceptin notwithstanding minor differences in clinically inactive components;*
- A sufficiently robust analytical bridge was established between ABP 980, US-licensed Herceptin, and EU-approved Herceptin to support the use of EU-Approved Herceptin as a comparator in clinical trial 20120283.*

Category	Test		Tier	Number of Lots (ABP 980: US Licensed H Herceptin: EU-Approved Herceptin)	US-Licensed Herceptin Range	ABP 980 Range	EU-Approved Herceptin Range
Primary Structure	Molecular Mass	Intact mass	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		Reduced/Deglycosylated Mass	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		Reduced Peptide Map	3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		Non-reduced peptide Map	3	4:2:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Glycan Map	% Afucosylation	2	22:23:33	5.1 - 8.6	7.6 - 9.1	5.1 - 9.2

		% High Mannose	2	22:23:33	2.1 - 6.5	1.5 - 4.2	1.8 - 4.8
		% Afucosylated Galactosylation	2	22:23:33	0.9 - 3.2	2.4 - 3.3	0.8 - 3.5
		% Galactosylation	2	22:23:33	21.8 - 53.4	42.7 - 57.0	22.0 - 51.4
		% Sialylation	3	22:23:33	1.2 - 2.4	0.8 - 1.7	1.1 - 2.6
	cIEF	Isoelectric point	2	4:3:3	8.8 - 8.9	8.8 - 8.9	8.8 - 8.9
		Isoelectric profile	3		Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Extinction coefficient (mg ⁻¹ cm ⁻¹)		2	1:1:1	1.57	1.55	1.54
	Identity by ELISA		3	4:1:1	All positive	All positive	All positive
	Higher Order Structure	FTIR	FTIR profile	3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin
			% Spectral similarity	2	7:6:6	99.3 - 100	99.5 - 100
		Near UV	UV profile	3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980

		% Spectral similarity	2	7:6:6	97.3 – 98.7	97.2 – 99.3	97.1 – 99.4
	DSC	DSC profile	3	11:9:9	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		Tm1 (°C) Tm2 (°C)	2	11:9:9	70.7 – 71.0 82.5 – 82.6	70.6 – 70.9 82.5 – 82.7	70.7 – 71.0 82.5 – 82.6
Particles and Aggregates	HIAC	≥ 2 µm particles	3	30:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		≥ 5 µm particles		30:6:6			
		≥ 10 µm particles		30:6:6			
		≥ 25 µm particles		30:6:6			
	MFI:	≥ 5 µm particles	3	15:7:7	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
		≥ 5 µm non-spherical particles	2	15:7:7	64 - 330	0 - 52	26 - 108
	FFF: Submicron particles		3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	DLS: Submicron particles		3	7:6:6	Visually Similar to ABP 980 and	Visually Similar to US-Licensed	Visually Similar to US-Licensed

					EU-Approved Herceptin	Herceptin and EU-Approved Herceptin	Herceptin and ABP 980
	SV-AUC:	SV-AUC Profile	3	11:9:9	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
		% HMW	2	11:9:9	<LOQ	<LOQ	<LOQ
	SE- HPLC-LS Molar mass	Molar mass	2	7:6:6	144 -148 KDa (main) 283-313 KDa (Pre-Peak)	144 -148 KDa (main) 281-318 KDa (Pre-Peak)	143 -148 KDa (main) 281-314 KDa (Pre-Peak)
		LS profile	3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
Product Related Substances and Impurities	SE- UHPLC % HMW	% HMW	2	13:21:33	0.3-1.1	0.6-1.1	0.4-1.2
		% Main peak	2		98.8-99.6	98.7-99.2	98.8-99.6
		SE-UHPLC profile	3		Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
	rCE-SDS	% HC+ LC	2	13:21:33	97.9-98.8	98.2-99.0	98.1-99.0
		% NGHC	2	13:21:33	0.6-0.9	0.2-0.5	0.6-1.0
		% LMW + MMW	2	13:21:33	0.3-1.0	0.5-1.0	0.3-0.7
		rCE-SDS profile	3	13:21:33	Visually Similar to ABP 980 and	Visually Similar to US- Licensed Herceptin and	Visually Similar to US- Licensed

					EU-Approved Herceptin	EU-Approved Herceptin	Herceptin and ABP 980
	nrCE- SDS:	% Main peak	2	13:21:33	98.7-99.2	98.2-98.6	98.5-99.0
		% Pre peaks	2	13:21:33	0.8-1.3%	1.4-1.8%	1.0%-1.5%
		nrCE-SDS profile	3	13:21:33	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
	CEX- HPLC	% Acidic peaks	2	13:21:33	24.8-32.1	33.1-39.9	23.1-32.6
		% Main peak	2	13:21:33	56.4-62.3	50.8-57.4	56.4-64.8
		% Basic peaks	2	13:21:33	10.4-13.6	8.6-12.1	10.4-14.1
		CEX-HPLC profile	3	13:21:33	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
Thermal Degradation	50°C (4 weeks)	SE-UHPLC rCE-SDS nrCE-SDS CEX-HPLC Potency (Bioassay)	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980
General Properties	Protein concentration (mg/mL)		2	29:21:30	20.6 to 21.6	20 to 21.4	20.4-21.3
	Protein content (mg/vial)		3	29:21:30	424 to 447	422 to 441 148 to 157	150 to 159
	Reconstitution time (s)		3	30:3:3	74-79	18-93	45-47
Process- Related Impurities	HCP-ELISA (ng/mg)		3	22:3:3	< 1	6-12	< 1
	HCP-2D-LC/MS		3	1:1:1	Visually Similar Low Level HCP to	Visually Similar Low Level HCP to	Visually Similar Low Level HCP to

				ABP 980 and EU-Approved Herceptin	US-Licensed Herceptin and EU-Approved Herceptin	US-Licensed Herceptin and ABP 980
	Protein A (ng/mg)	3	22:3:3	< 1	< 1	< 1
	Residual DNA (pg/mg)	3	10:3:3	< 0.2	< 0.2	< 0.2
Biological Activity	Proliferation inhibition bioassay (%)	1	22:23:33	88-121	96-122	88-124
	HER2 binding (%)	1/2	22:23:33	90-117	86-109	85-119
	Induction of ADCC (%), PBMC Method	1	22:23:33	51-115	82-124	35-119
	Induction of ADCC (%), NK92 Method	1	22:23:33	36-106	79-117	46-143
	FcγRIIIa (158V) binding (%)	2	22:23:33	48-120	86-112	48-104
	FcγRIIIa (158F) binding (%)	2	12:14:11	51-105	97-110	51-115
	FcRn binding (%)	2	22:22:33	78-108	93-116	86-106
	Induction of CDC	3	1:1:1	Visually Similar Lack of CDC Activity to ABP 980 and EU-Approved Herceptin	Visually Similar Lack of CDC Activity to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar Lack of CDC Activity to US-Licensed Herceptin and ABP 980
	C1q binding (%)	3	11:10:10	83-108	98-134	72-102
	Binding kinetics to HER2 by SPR	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US- Licensed Herceptin and ABP 980

	Inhibition of AKT phosphorylation (% inhibition dose-response curve)	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Inhibition of proliferation in NCI-N87 Cells (% inhibition dose-response curve)	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Inhibition of proliferation: synergy with chemotherapeutic (% inhibition dose-response curve)	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Lack of inhibition of proliferation in non-amplified HER2 cells (% inhibition dose-response curve)	3	4:3:3	No inhibition of proliferation detected	No inhibition of proliferation detected	No inhibition of proliferation detected
	Lack of ADCC in HER2 Negative cells	3	1:1:1	No ADCC detected	No ADCC detected	No ADCC detected
	FcγRIa binding by SPR	3	4:3:3	Visually Similar Sensorgrams to ABP 980 and EU-Approved Herceptin	Visually Similar Sensorgrams to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar Sensorgrams to US-Licensed Herceptin and ABP 980
	FcγRIIb binding by SPR	3	4:3:3	Visually Similar Sensorgrams	Visually Similar Sensorgrams	Visually Similar Sensorgrams

				to ABP 980 and EU-Approved Herceptin	to US-Licensed Herceptin and EU-Approved Herceptin	to US-Licensed Herceptin and ABP 980
	FcγRIIIb binding by SPR	3	4:3:3	Visually Similar Sensorgrams to ABP 980 and EU-Approved Herceptin	Visually Similar Sensorgrams to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar Sensorgrams to US-Licensed Herceptin and ABP 980
	FcγRIIa (131H) binding (%)	3	16:13:13	81-106	90-103	85-108
	FcγR Binding on Primary Macrophages by FACS	3	4:3:3	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980
	Antibody-dependent cellular phagocytosis (ADCP) by FACS	3	7:6:6	Visually Similar to ABP 980 and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and EU-Approved Herceptin	Visually Similar to US-Licensed Herceptin and ABP 980

3.2.R.1.1 Primary Structure

The similarity of primary structures among ABP 980, US-licensed Herceptin, and EU-approved Herceptin were assessed as follows:

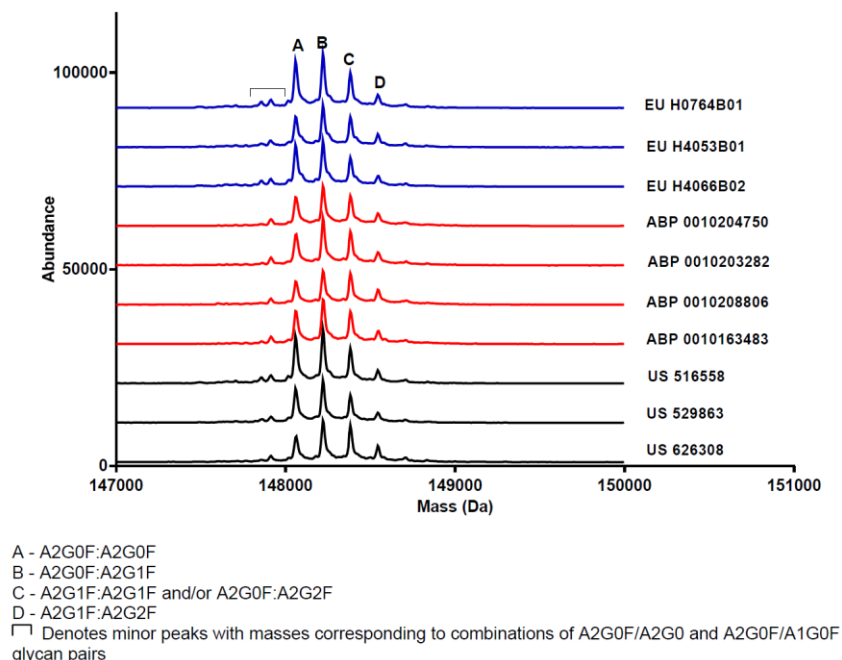
- The intact and reduced molecular mass was analyzed by electrospray ionization-time of flight-mass spectrometer (ESI-TOF-MS).
- The amino acid sequence, disulfide structure, and post-translational modifications were assessed by reduced and non-reduced peptide mapping.
- N-linked glycosylation profiles were analyzed by hydrophilic interaction liquid chromatography (HILIC).
- Isoelectric point (PI) was determined by capillary isoelectric focusing (cIEF).
- Extinction coefficient was determined by amino acid analysis (AAA).
- Identity test by an enzyme-linked immunosorbent assay (ELISA)

Reviewer Comment: Data provided regarding assessment of the primary structures support similarity of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. In addition to the Tier 3 assessment reviewed below, some primary structure attributes (intact mass, reduced and deglycosylated mass, amino acid sequence by peptide map, and disulfide-linked peptide fragment mass by non-reduced peptide map) were assessed using the Tier 2 expectation approach that compares quantitative differences in observed and theoretical molecular masses and evaluates them against criteria based on method capability. All molecular mass attributes evaluated by this Tier 2 criteria were reviewed and found to lie well within the similarity assessment criteria.

3.2.R.1.1.1 Intact molecular Mass (4:3:3)

The intact molecular mass analysis was performed for three lots for each of US-licensed Herceptin and EU-approved Herceptin, and four ABP 980 clinical lots by ESI-TOF-MS. Four ABP 980 lots analyzed include three 150 mg lots and one 420 mg lot (referred to in the submission as 440 mg). A comparison of the profiles is shown below. The mass profiles for the three products are visually similar. The major and minor species observed are consistent among three products, supporting product similarity with respect to amino acid composition, glycosylation, and glycan distribution. The four major species shown in Peaks A-D are different glycan forms. Each of the 4 major glycans are asialylated core-fucosylated biantennary complex oligosaccharides that differ in number of terminal galactose molecules. No new species were observed in ABP 980 lots.

Figure 1. Intact Molecular Mass for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

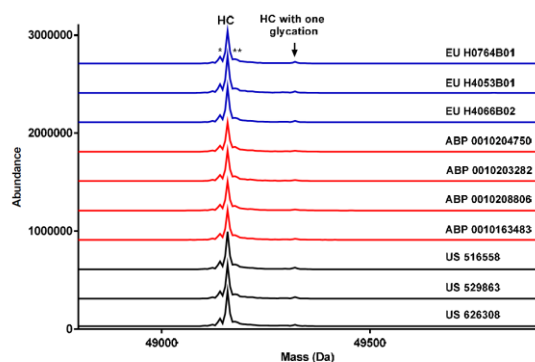


Reviewer Comment: The data provided support the conclusion of identical primary sequences between ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.1.2 Reduced and Deglycosylated Molecular Masses of HC and LC using ESI-TOF-MS (4:3:3)

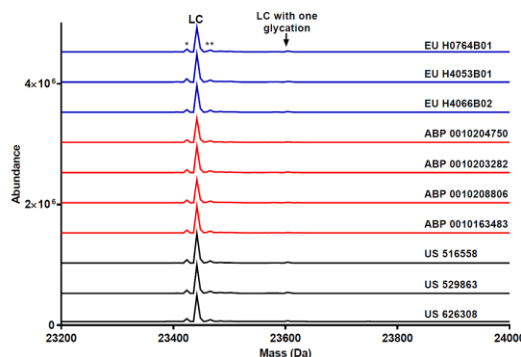
In addition to the assessment of the intact molecular mass, the reduced and deglycosylated molecular mass was assessed for the same lots of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Mass profiles were assessed following removal of N-linked glycans by PNGase F treatment and reduction of disulfides. The results demonstrate that the reduced and deglycosylated LC and HC masses of ABP 980 are similar to those of US-licensed Herceptin and EU-approved Herceptin. No new species were observed in ABP 980 lots. Figure 2 and 3 below show the mass profiles for heavy and light chains, respectively.

Figure 2. Comparison of Reduced and Deglycosylated Heavy Chain Mass Profiles for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



HC = heavy chain; *, ** = Mass spectrometry ionization artifacts related to loss of water at lower mass and salt adducts at higher mass respectively

Figure 3. Comparison of Reduced and Deglycosylated Light Chain Mass Profiles for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



LC = light chain
LC = light chain; *, ** = Mass spectrometry ionization artifacts related to loss of water at lower mass and salt adducts at higher mass respectively.

Reviewer Comment: Intact mass, as well as deglycosylated and reduced mass data support similar primary structures among ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.1.3 Reduced Peptide Map (7:6:6)

The reduced peptide map was performed side-by-side for ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The 7 ABP 980 lots include three 150 mg clinical lots, one 420 mg clinical lot and three 420 mg validation lots. Representative images of the peptide maps were copied directly from the submission and are shown below. All of the overlays showed similar peak profiles for the 3 products with 100% coverage observed, and no new peaks above the integrity limit ($10 \times$ noise levels) were detected in ABP 980. The differences between the observed and theoretical masses for all tryptic peptides were well within 50 ppm for all 3 products. ABP 980 lacks the C-terminal lysine by design, while low levels of C-terminal lysine ($\leq 1\%$) were detected in US-licensed Herceptin and EU-approved Herceptin lots. Examination of the amino acid sequence revealed a single consensus site for N-linked glycosylation located on the heavy chain at Asn300 in all ABP 980, US-licensed Herceptin, and EU-approved Herceptin peptide maps. Two sequence variants (T259A, N84T) were identified for ABP 980 at levels of approximately 1% or less, whereas one sequence variant (I34M) was observed in the HC CDR of US-licensed Herceptin and EU-approved Herceptin at approximately 1% or less. The levels of Asp deamidation are consistent among lots tested. Slightly higher levels of methionine oxidation in ABP 980 ($\leq 4\%$) were observed compared to US-licensed Herceptin, and EU-approved Herceptin.

Figure 4. Reduced Tryptic Peptide Map for Trastuzumab (EU), ABP 980 (Clinical), and Trastuzumab (US)
Time: 0 to 64 minutes

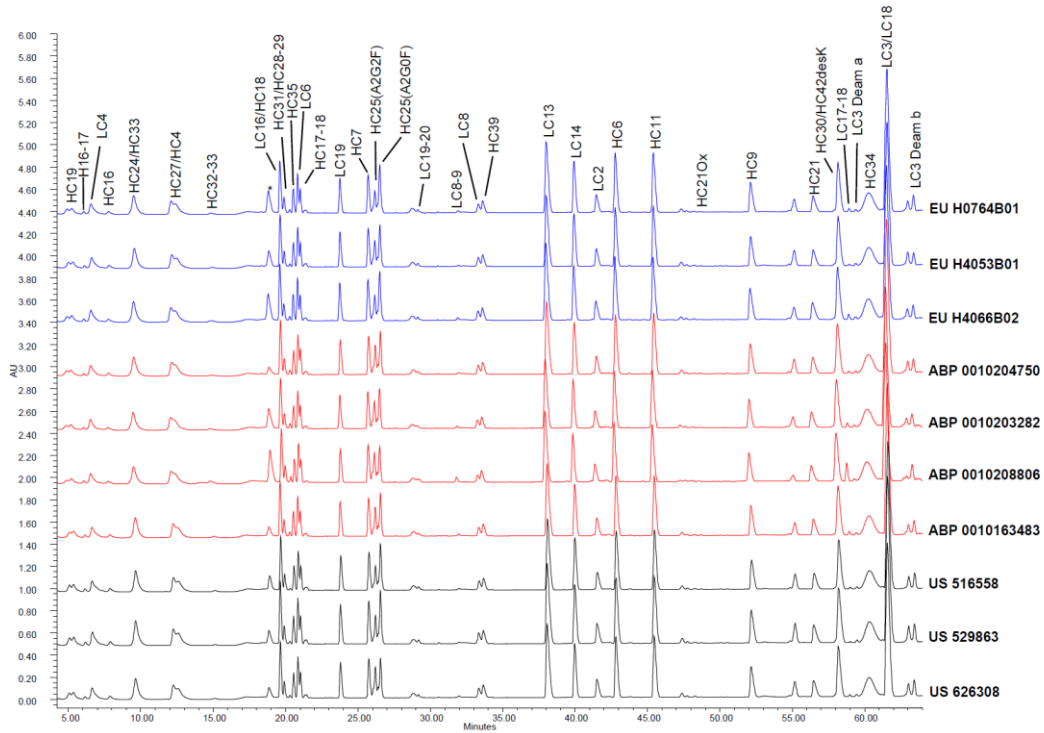
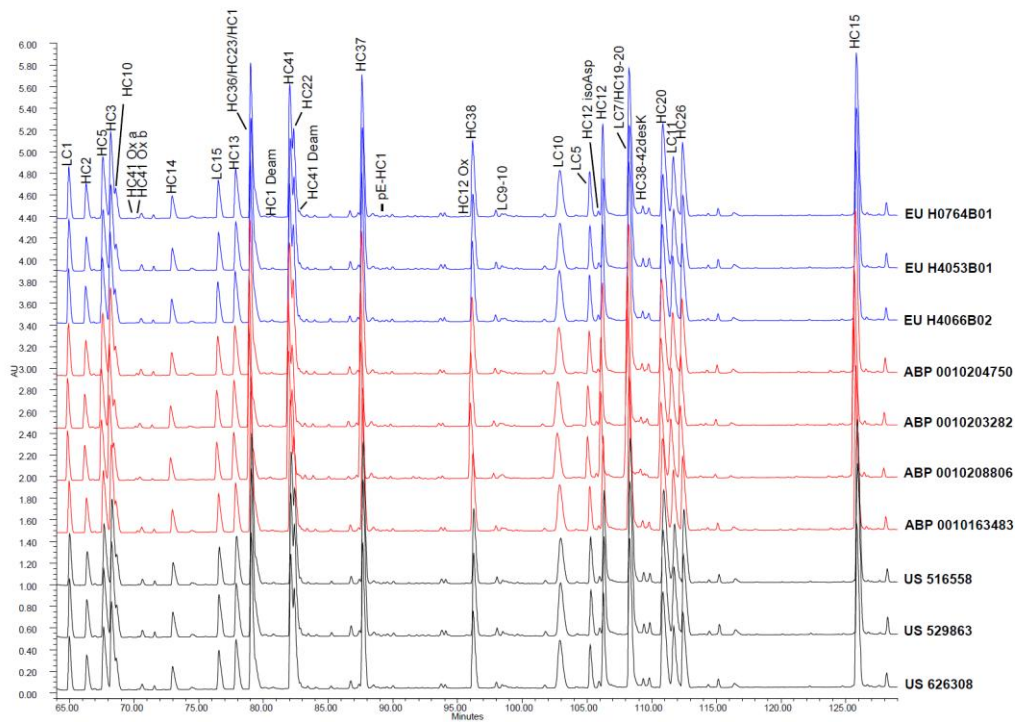


Figure 4. Reduced Tryptic Peptide Map for Trastuzumab (EU), ABP 980 (Clinical), and Trastuzumab (US)
Time: 64 to 130 minutes



Reviewer Comment: Due to the low levels observed, the differences regarding C-terminal lysine, sequence variants, methionine oxidation, and Asp deamidation between ABP 980, US-licensed Herceptin and EU-approved Herceptin do not preclude a demonstration that ABP 980 is highly similar to US-licensed Herceptin. Only small differences in C-terminal lysine were observed, it's known that these residues are rapidly cleaved by carboxypeptidases after administration. The ABP 980 sequence variants T259A and N84T are located outside the CDR in the V_H and C_H2 domains, respectively, and therefore unlikely to impact functional activity of the molecule. Methionine oxidation levels in ABP 980 lots are 4% for M²⁵⁵ and 1-2% for M⁴³¹, which are ~1-2% higher than the levels observed at these residues in US-licensed and EU-approved Herceptin. Collectively, these minor differences in sequence variants and post-translational modifications occur at low levels that pose negligible risk to impact functional activity of the molecule. Additionally, data from functional assays as part of the biological activity similarity assessment (refer to biological activity section below) support that these differences do not preclude a demonstration that ABP 980 is highly similar to US-licensed Herceptin.

The observed molecular masses demonstrate similarity of ABP 980, US-licensed Herceptin and EU-approved Herceptin in terms of the amino acid sequence and post-translational modifications

3.2.R.1.1.4 Disulfide Structure – Non-reduced Peptide Map (4:2:3)

Non-reduced peptide map was used to assess the disulfide bonds. Four lots of ABP 980, including three 150 mg clinical lots and one 420 mg clinical lot, two lots of US-licensed Herceptin, and three lots of EU-approved Herceptin were tested. The sponsor provided peptide map chromatograms (reduced and non-reduced) for the side-by-side comparison (not reproduced here). The differences between the observed and theoretical masses for these cysteine-containing peptides are within 50 ppm for all 3 products, which is within method variability. The expected and equivalent (for an IgG1 antibody) disulfide linkage was observed among ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

Reviewer Comment: Non-reduced peptide map data provided support the conclusion that all three products have the same disulfide structures.

3.2.R.1.1.5 Glycan Map (22:23:33)

Hydrophilic liquid interaction chromatography (HILIC) is used to assess the N-linked glycosylation profile for ABP 980, US-licensed Herceptin, and EU-approved Herceptin. In total, 22 lots of ABP 980, 23 lots of US-licensed Herceptin, and 33 lots EU-approved Herceptin were included in the similarity assessment. The relative amounts of the individual glycan species for all lots of three products tested are provided in the submission. Representative chromatograms from two side-by-side experiments for 7 lots of ABP 980, 6 lots each of US-licensed Herceptin and EU-approved Herceptin, are copied from the submission.

Reviewer Comment: The HILIC method is proposed as a specification test for ABP 980. Information regarding the assay procedure and assay validation are described in section 3.2.S.4.2 and section 3.2.S.4.3, respectively.

Figure 8. HILIC Glycan Map for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

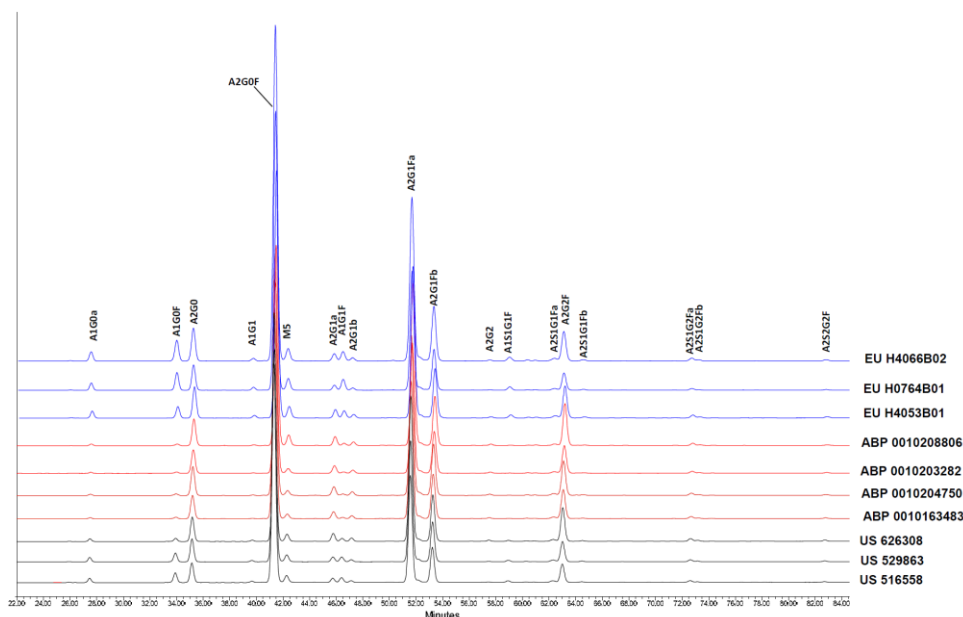
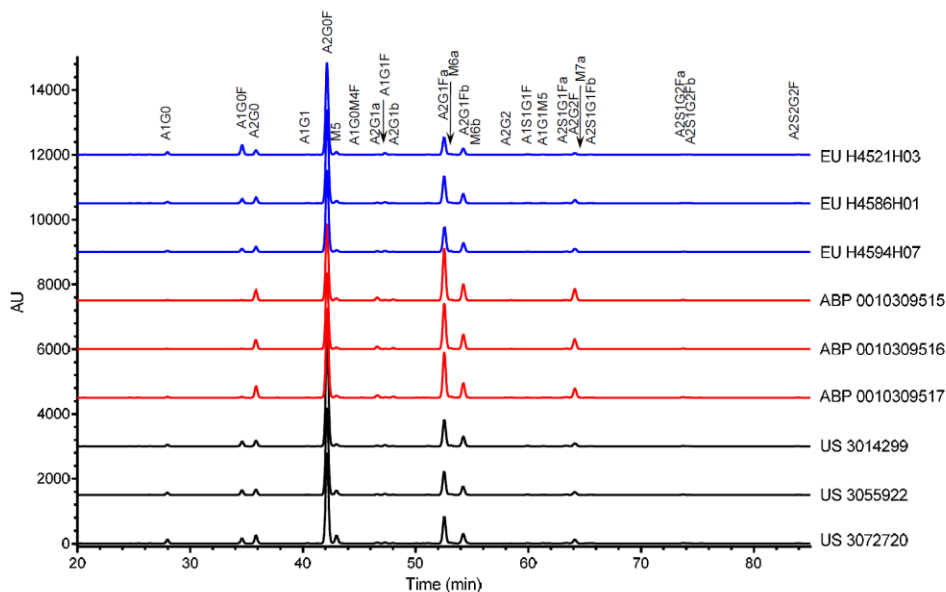


Figure 9. HILIC Glycan Map for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The overlay shows that three products have similar profiles with the same glycans present in consistent but slightly different ratios. No new or missing peaks observed among three products. According to literature reports, IgG1 effector functions (e.g., ADCC), which are mediated by FcγRIIIa, are indirectly linked to afucosylation, high mannose, galactosylation, and sialylation. Additionally, the levels of high mannose and sialylated species are relevant to product serum half-life through differential clearance. Therefore, the following glycan groups in ABP 980, US-licensed Herceptin, and EU-approved Herceptin were evaluated as Tier 2 attributes, based on their potential to impact IgG1 effector functions and/or PK:

- **% Afucosylation**, which includes afucosylated complex and hybrid glycans lacking core fucose
% Afucosylation

$$= \%A1G0a + \%A1G0b + \%A1G1 + \%A2G0 + \%A2G1a + \%A2G1b \\ + \%A2G2 + \%A1G0M4 + \%A1G0M5 + \%A1G1M4 + \%A1G1M5$$

- **% High mannose**, which includes high mannose glycans, M5 through M9

$$\% \text{ High Mannose} = \%M5 + \%M6 + \%M7 + \%M8 + \%M9$$

- **% Galactosylation**, which includes complex and hybrid glycans containing at least 1 terminal galactose

$$\% \text{ Galactosylation} = \%A1G1(a) + A1G1F(a) + A1G1F(b) + \%A2G1(b) + \%A2G1F(a) + \%A2G1F(b) + \\ \%A1G1M4F + \%A3G1F + \%A1G1M5 + \%A2G2F + \%A1G1M5F + \%A2S1G2F$$

- **% Afucosylation-galactosylation**, which includes complex and hybrid structures lacking core fucose, but containing at least 1 terminal galactose

$$\% \text{ Afucosylated galactosylation} \\ = \%A1G1 + \%A2G1a + \%A2G1b + \%A2G2 + \%A1G1M4 + \%A1G1M5$$

Considering that sialylation has a low potential to impact ADCC, and low level of sialylated species ($\leq 2.6\%$) were observed in all three products, therefore sialylation is considered a Tier 3 attribute.

- **% Sialylation**, which has the potential to impact PK and ADCC

$$\% \text{ Sialylation} = \%A1G1S1F + \%A2G1S1Fa + \%A2G1S1Fb + \%A2G2S1Fa + \%A2G2S1Fb \\ + \%A2G2S2F$$

Reviewer Comment: *The proposed categories for glycan groups are considered appropriate.*

The results of glycan distribution for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots tested are shown below.

Figure 10. Afucosylation Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

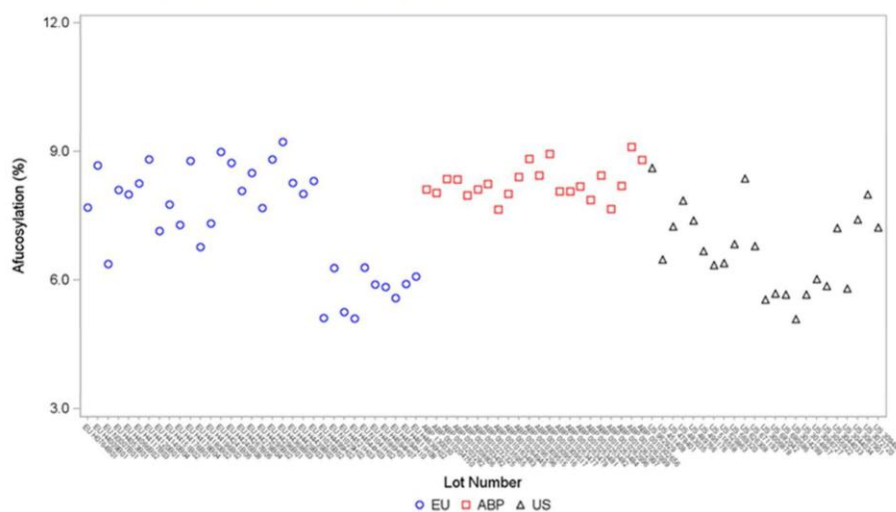


Figure 11. High Mannose Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

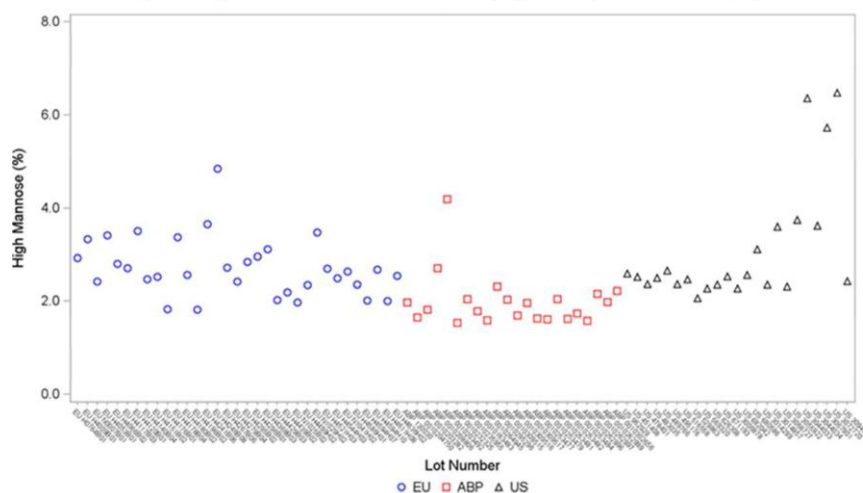


Figure 12. Galactosylation Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

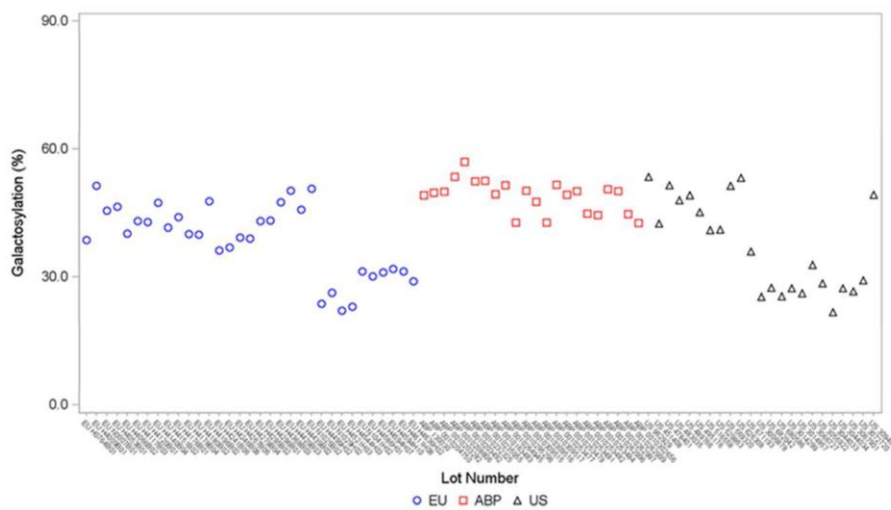


Figure 13. Afucosylated Galactosylation Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

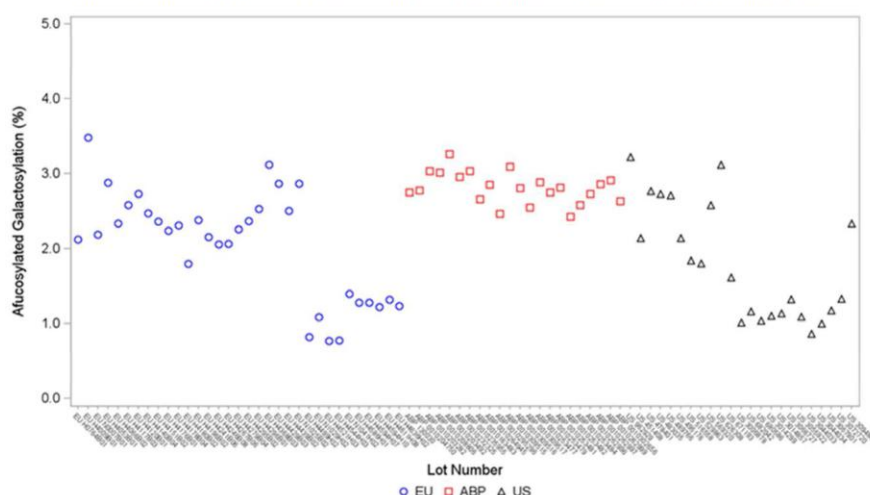
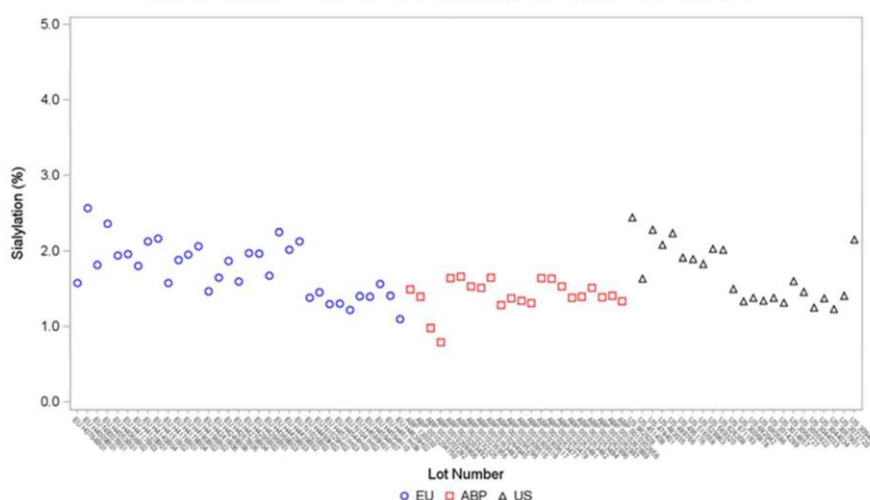


Figure 14. Sialylation Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The following conclusions are drawn:

- Compared to US licensed Herceptin and EU approved Herceptin, a relatively high degree of consistency was observed among ABP 980 lots tested regarding glycan distribution throughout the similarity assessment. The following ranges were observed for lots of ABP 980: afucosylation (7.6-9.1%), high mannose (1.5-4.2%), galactosylation (42.7-57%), afucosylated galactosylation (2.4-3.3%), and sialylation (0.8-1.7%).
- For US-licensed Herceptin and EU-approved Herceptin lots, apparent temporal trends are observed in the data for afucosylation, galactosylation, and afucosylated galactosylation. Relatively lower levels of these glycan species are observed for a period of time. Additionally, for US-licensed Herceptin, relatively higher levels of high mannose are observed for a period of time.

A previous study (Kim, et.al. MABS. 2017. 9(4):704) found decreased levels of % afucose (G0+G1+G2) in US-licensed Herceptin and EU-approved Herceptin lots with expiry dates of August 2018 or later, resulting in a downward trend in FcγRIIIa binding and ADCC activity. Amgen's results of glycan distribution are corroborated by this previous report.

Comparisons of each glycan group among the three products are shown in the figures below. The quality ranges of US-licensed Herceptin or EU-approved Herceptin (Mean $\pm$ 3SD) for each glycan group are provided as red dotted lines on the figures. These quality ranges were used for similarity assessment.

Afucosylation

Figure 15. Afucosylation- ABP 980 Compared to Trastuzumab (US) Quality Range

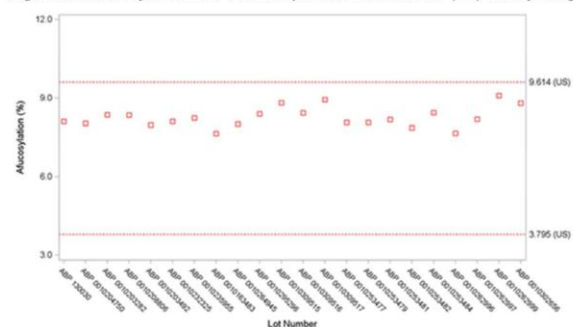


Figure 19. Total Afucosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range

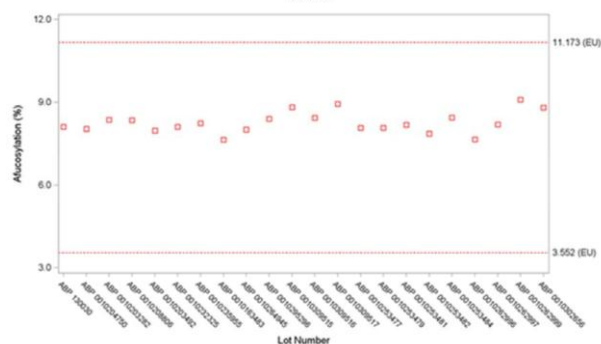
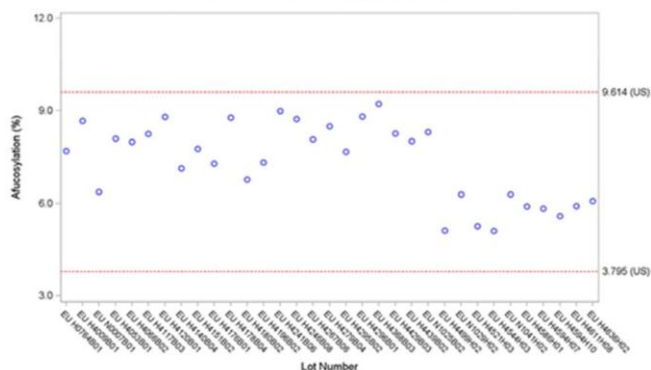


Figure 23. Total Afucosylation - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



High Mannose

Figure 16. High Mannose - ABP 980 Compared to Trastuzumab (US) Quality Range

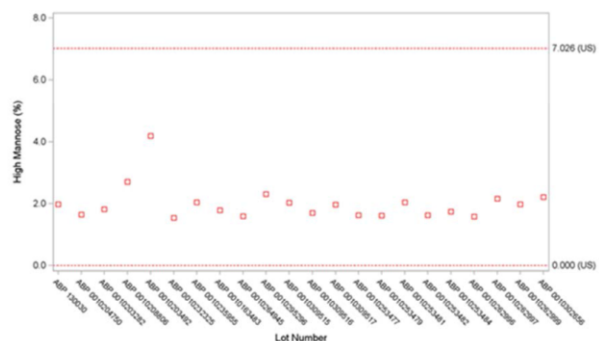


Figure 20. High Mannose - ABP 980 Compared to Trastuzumab (EU) Quality Range

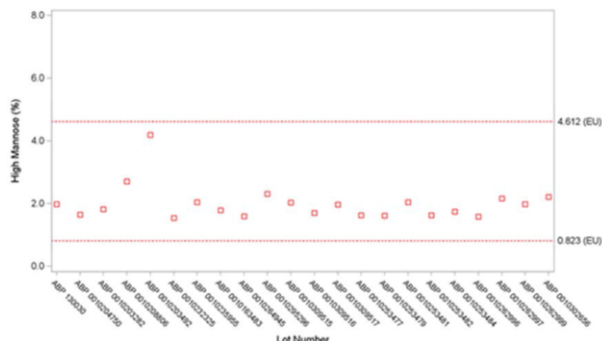
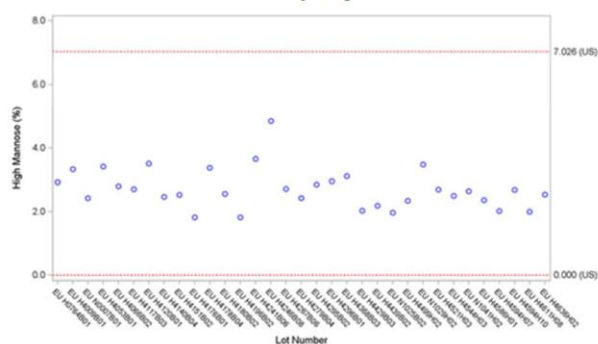


Figure 24. High Mannose - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Galactosylation

Figure 17. Galactosylation - ABP 980 Compared to Trastuzumab (US) Quality Range

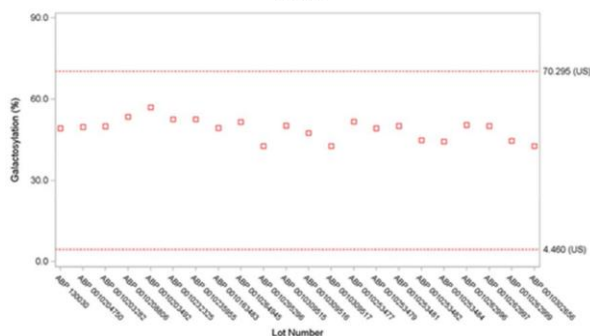


Figure 21. Galactosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range

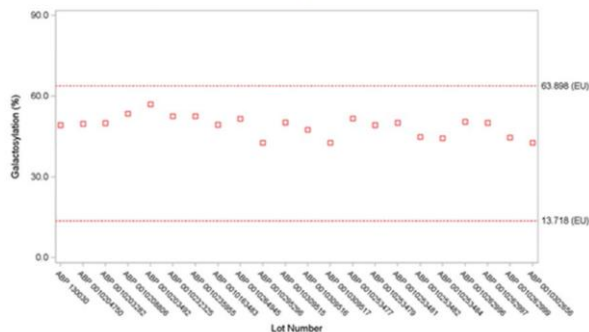
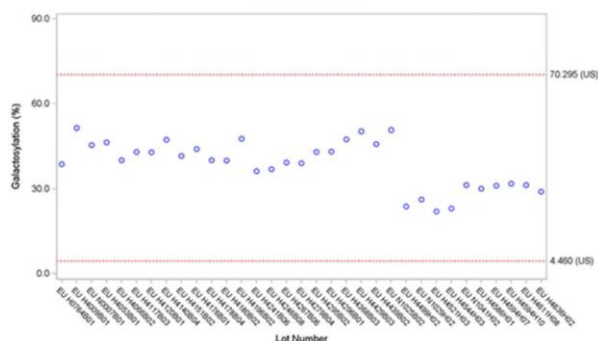


Figure 25. Galactosylation - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Afucosylation-galactosylation

Figure 18. Afucosylated Galactosylation - ABP 980 Compared to Trastuzumab (US) Quality Range

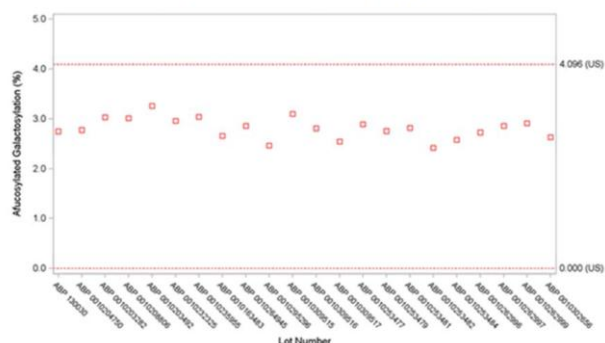


Figure 22. Afucosylated Galactosylation - ABP 980 Compared to Trastuzumab (EU) Quality Range

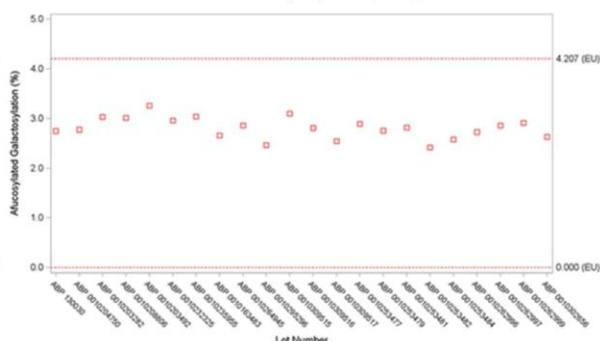
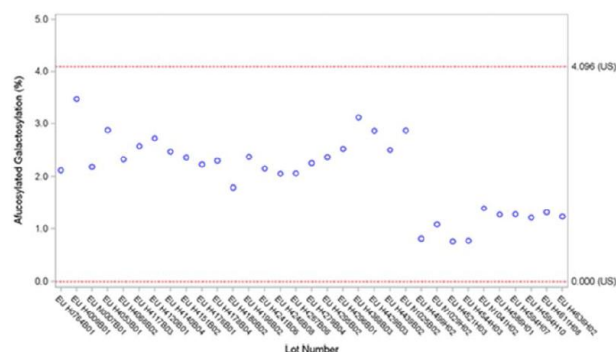


Figure 26. Afucosylated Galactosylation – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Sialylation

Sialylation was evaluated by Tier 3 criteria. There are similarly low levels of sialylation ($\leq 2.6\%$) in ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots.

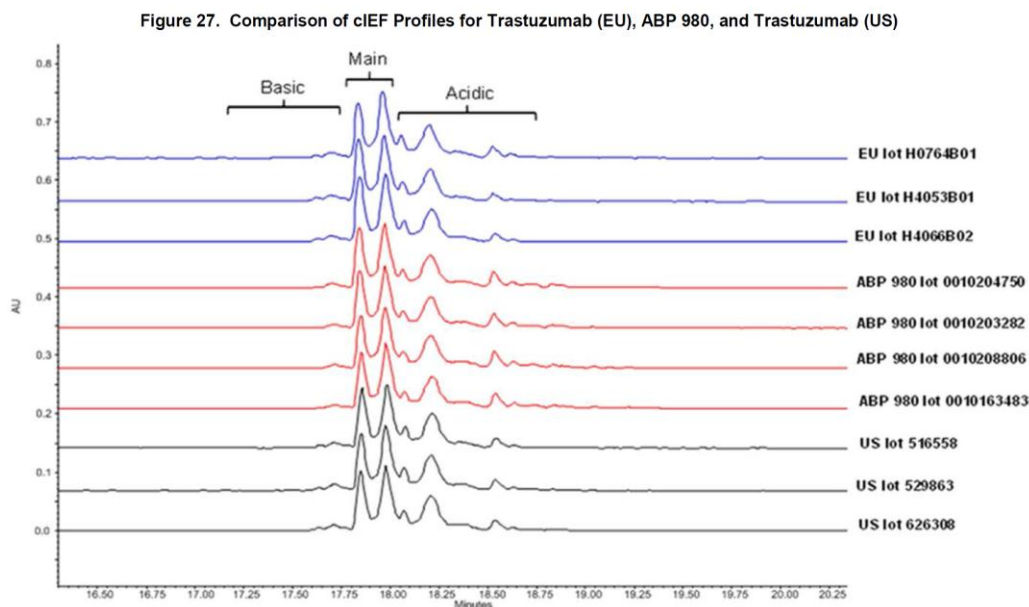
Reviewer Comment: The results support similar glycan profiles and content among ABP 980, US-licensed Herceptin and EU-approved Herceptin. The following conclusions are drawn for the glycosylation profile comparison among the three products:

- The glycan map profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots are visually similar.
- Regarding afucosylation, high mannose, and galactosylation, all results for the ABP 980 lots are within the quality range of US-licensed Herceptin and EU-approved Herceptin. The results for EU-approved Herceptin also fall within the quality range of US-licensed Herceptin.
- Levels of sialylation for ABP 980 (0.8%-1.7%, Mean: 1.42%) are relatively lower to both US-licensed Herceptin (1.2%-2.4%, Mean: 1.7%) and EU-approved Herceptin (1.1%-2.6%, Mean: 1.76). The effects of sialylation on ADCC and PK are likely negligible at these low levels. Given that the differences in sialylation are small ($< 1\%$), functional data address residual uncertainty. The results from FcγRIIIa and FcRn binding (refer to the section below) support similar behavior among three products. Therefore, the difference observed in sialylation does not

preclude a determination that ABP 980 is highly similar to US-licensed Herceptin or the establishment of the analytical bridge.

3.2.R.1.1.6 Isoelectric Point (4:3:3)

Capillary Isoelectric Focusing (cIEF) was performed on 4 lots of ABP 980, 3 lots of US-licensed Herceptin, and 3 lots of EU-approved Herceptin in a side-by-side manner. For similarity assessment, the isoelectric point is evaluated as a Tier 2 attribute, while the isoelectric focusing profile is evaluated as a Tier 3 attribute. A comparison of the cIEF profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin is provided in Figure 27 shown below. All lots tested exhibit two main peaks (peak 1 and peak 2) similar in height. The cIEF profiles are similar with minor differences in basic and acidic regions. The pI values of main peak 1 (8.8) and main peak 2 (8.9) are identical among three product lots, and close to the calculated theoretical pI of 9.0. No specific method qualification data was provided in the submission. The similarity acceptance criterion for pI allows for a difference of no more than 0.1 pI units between products, which is based on assay intermediate precision standard deviation of 0.04 pI units for the determination of main peak pI. Given that identical results were obtained for all lots, these data support the same isoelectric point for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.



Reviewer Comment: Amgen provided data supporting the conclusion that the distribution profiles and peak intensities of the cIEF electropherograms were similar among ABP 980, US-licensed Herceptin and EU-approved Herceptin. Quantitative evaluation of pI by Tier 2 criteria support a similar isoelectric point for ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Qualitative comparison of the cIEF profiles support visually highly similar electropherograms. One minor peak in the basic region is observed in US-licensed and EU-approved Herceptin lots that corresponds to C-terminal lysine not present in ABP 980. As noted elsewhere in this review, differences in C-terminal lysine are justified based on current understanding that C-terminal lysine residues of monoclonal antibodies are cleaved in the bloodstream shortly after intravenous administration. Potential minor

quantitative differences in basic and acidic regions measured by this method are similar to, and quantitatively evaluated by the orthogonal CEX-HPLC method (refer to the section below).

3.2.R.1.1.7 Extinction Coefficient (1:1:1)

The experimental extinction coefficient was determined on one lot each of ABP 980, US-licensed Herceptin and EU-approved Herceptin by amino acid analysis (AAA). The extinction coefficient is evaluated as a Tier 2 attribute. Amino acid composition does not vary from lot-to-lot, thus similarity is evaluated for only a single lot of each product compared against the theoretical value and range defined by method capability. The theoretical extinction coefficient is $1.50 \text{ cm}^{-1} (\text{mg/mL})^{-1}$ and results are assessed against the acceptance criterion of $\pm 10\%$ of the theoretical extinction coefficient, which is based on the intermediate precision of the AAA method. Briefly, samples were dialyzed into PBS and diluted to approximately 1 mg/mL. The absorbance at 280 nm was measured for the samples using a calibrated UV spectrophotometer. Three aliquots of each sample were subjected to vapor phase hydrolysis with boiling hydrochloric acid. The hydrolyzed samples were then reconstituted in sample dilution buffer, and the resulting amino acids were quantified by strong cation exchange chromatography and post-column derivatization with ninhydrin using an amino acid analyzer. Triplicate measurements were performed. The experimentally-determined extinction coefficients for ABP 980, trastuzumab (US), and trastuzumab (EU) are provided in Table 16 below.

Table 16. Experimental Extinction Coefficient Determination of Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	Extinction coefficient ($\text{mg}^{-1} \cdot \text{cm}^{-1} \cdot \text{mL}$)	Lot Number	Extinction coefficient ($\text{mg}^{-1} \cdot \text{cm}^{-1} \cdot \text{mL}$)	Lot Number	Extinction coefficient ($\text{mg}^{-1} \cdot \text{cm}^{-1} \cdot \text{mL}$)
EU H0764B01	1.54	ABP 0010203282	1.55	US 529863	1.57

Reviewer Comment: *ABP 980 has a similar experimentally-determined extinction coefficient compared to US-licensed Herceptin and EU-approved Herceptin.*

3.2.R.1.1.8 Identity by ELISA (4:1:1)

An enzyme-linked immunosorbent assay (ELISA) is used as the identity test. The analytical procedure is detailed in 3.2.S.4.2 and is proposed for release of DS and DP. Identity test is considered a Tier 3 attribute for similarity assessment. Four ABP 980 lots were compared with one lot each of US-licensed Herceptin and EU-approved Herceptin.

Table 17. Identity ELISA Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	Result ^a	Lot Number	Result ^a	Lot Number	Result ^a
EU H0764B01	Pass	ABP 0010204750	Pass	US 529863	Pass
		ABP 0010203282	Pass		
		ABP 0010208806	Pass		
		ABP 0010163483	Pass		

^a "Pass" is defined as an optical absorbance signal-to-background ratio for sample replicates of ≥ 10.0 .

Reviewer Comment: *The method was demonstrated to be sufficient to discriminate against other antibody products manufactured by Amgen. The data support similarity for this attribute between ABP 980, US-licensed Herceptin, and EU-approved Herceptin.*

3.2.R.1.2 Higher Order Structure

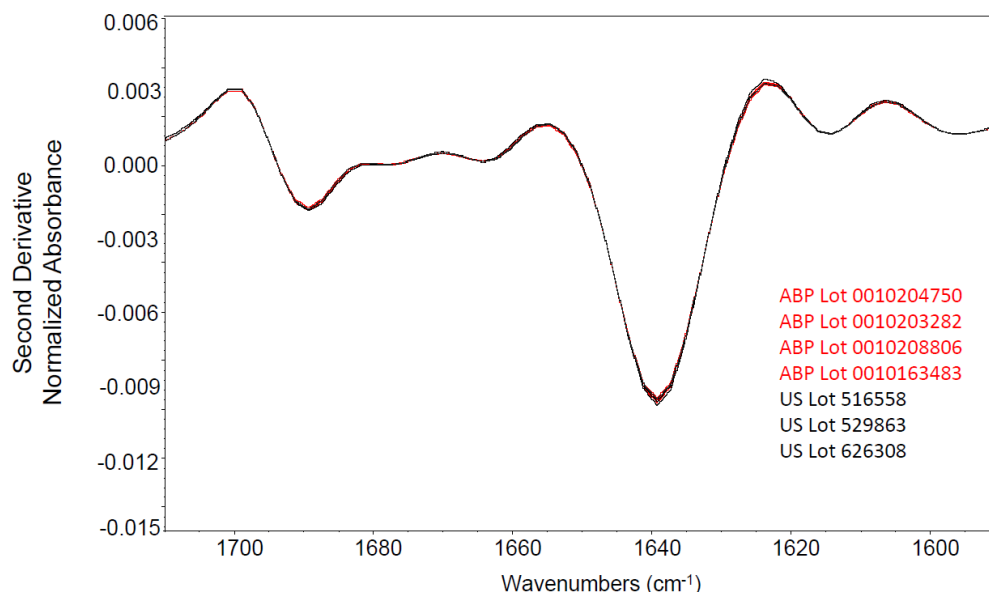
The similarity of higher order structures of ABP 980, US-licensed Herceptin, and EU-approved Herceptin were assessed as follows:

- The secondary structure was analyzed by Fourier-transformed infrared (FTIR) spectroscopy.
- The tertiary structure was assessed by near ultraviolet (UV) circular dichroism (CD) spectroscopy.
- The thermal stability and the overall conformation of the proteins were analyzed by differential scanning calorimetry (DSC).

3.2.R.1.2.1 FTIR (7:6:6)

The FTIR was performed on 7 ABP 980 lots, and 6 lots each of US-licensed Herceptin and EU-approved Herceptin in two side-by-side experiments. The 7 ABP 980 lots include clinical (150 mg and 420 mg presentations) and validation lots (420 mg presentation). For similarity assessment, the spectral similarity, which provides a quantitative determination within a defined wavenumber region (1600 to 1700 cm^{-1}), is classified as a Tier 2 attribute; whereas FTIR profile comparison is considered a Tier 3. The acceptance criterion of $\geq 95\%$ for spectral similarity was determined based on method capability. FTIR spectra measured for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots were compared to US-licensed Herceptin and EU-approved Herceptin. The sponsor submitted spectral similarity calculations for the three products and all results showed $\geq 99.3\%$ spectral similarity, which are well within the 95% criterion). The second derivative spectra for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots were calculated using a 9 point smoothing of the original spectra and results are provided in the submission. The profiles are visually similar and exhibit typical IgG1 anti-parallel beta-sheet structure. A representative second derivative FTIR spectrum of ABP 980 is provided below.

Figure 1. Second Derivative FTIR Spectra Comparing ABP 980 Clinical Lots and Trastuzumab (US)

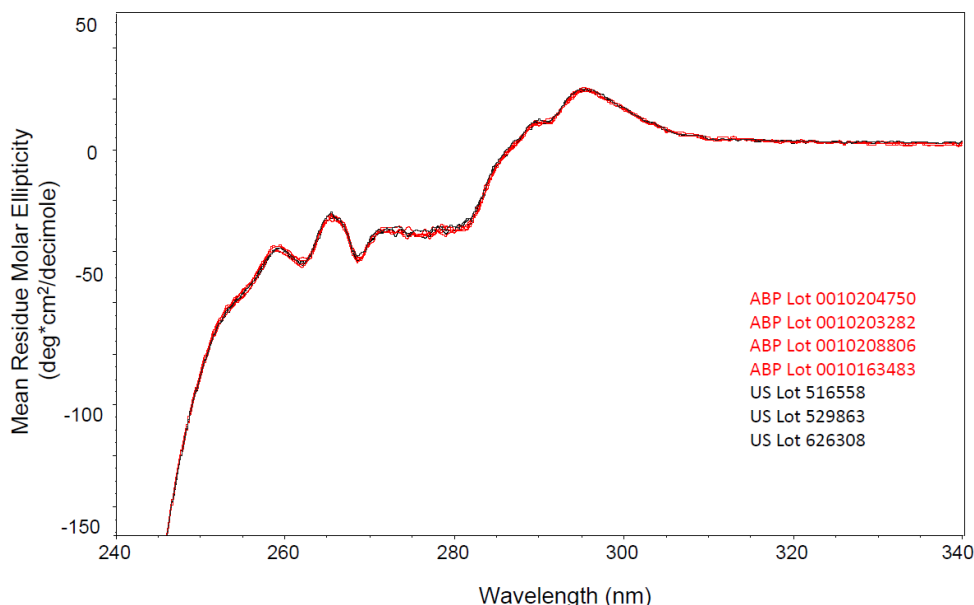


Reviewer Comment: The FTIR data sets provided by the applicant, both the reference comparison and the spectral overlays, support similar secondary structures between ABP 980, US-licensed Herceptin, , and EU-approved Herceptin.

3.2.R.1.2.2 Near Ultraviolet Circular Dichroism (7:6:6)

Near UV CD was performed on the same lots used for FTIR in side-by-side manner. The similarity assessment was performed on spectral similarity which is considered a Tier 2 attribute and near UV CD profile comparison which is considered a Tier 3 attribute. The spectral similarity calculations all measured $\geq 97.1\%$ for the three products, and thus met the similarity acceptance criterion of $\geq 95\%$ based on method capability. Comparison of the near UV CD spectra between ABP 980 and US-licensed Herceptin; ABP 980 and EU-approved Herceptin; US-licensed Herceptin and EU-approved Herceptin, indicates similar profiles. A representative near UV CD spectra of ABP 980 is provided below.

Figure 7. Near UV CD Spectra Comparing ABP 980 Clinical Lots and Trastuzumab (US)



Reviewer Comment: Data provided support that ABP 980, US-licensed Herceptin, and EU-approved Herceptin are similar in terms of tertiary structure.

3.2.R.1.2.3 Differential Scanning Calorimetry (DSC) (11:9:9)

The DSC method was performed on 11 lots of ABP 980 and 9 lots each of US-licensed Herceptin and EU-approved Herceptin. Testing was conducted in three side-by-side experiments for profile comparison. The DSC scans are visually similar for the three products. An overlay of the DSC scans for ABP 980, US-licensed Herceptin, and EU-approved Herceptin are shown below. The molecules exhibit 2 thermal transitions by DSC at approximately 70.9°C (Tm1) and 82.6°C (Tm2) that correspond to unfolding of CH2 and Fab/CH3 domains, respectively. Similarity assessments were performed on Tm1 and Tm2 by Tier 2 criteria, and on DSC thermogram profiles by qualitative Tier 3 criteria. Each ABP 980 lot was compared against the quality ranges (Mean $\pm$ 3xSD) established based on US-licensed Herceptin and EU-approved Herceptin lots, respectively. Additionally, each EU-approved Herceptin lot was assessed against the quality range of US-licensed Herceptin lots. All results fell within these quality ranges except for one ABP 980 lot (ABP 0010208806), which measured 0.1°C above the Tm2 quality range of US-licensed Herceptin (Figure 19 below).

Reviewer Comment: This slight difference in Tm2 does not preclude a determination that ABP 980 is highly similar to US-licensed Herceptin because >90% of the ABP 980 lots tested within the quality range of US-licensed Herceptin.

Figure 18. DSC T_{m1} - ABP 980 Compared to Trastuzumab (US) Quality Range

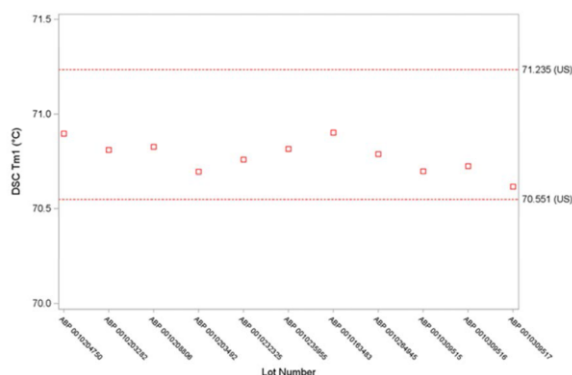


Figure 19. DSC T_{m2} - ABP 980 Compared to Trastuzumab (US) Quality Range

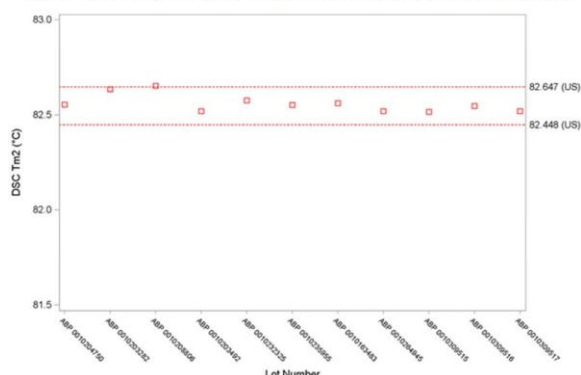


Figure 20. DSC T_{m1} - ABP 980 Compared to Trastuzumab (EU) Quality Range

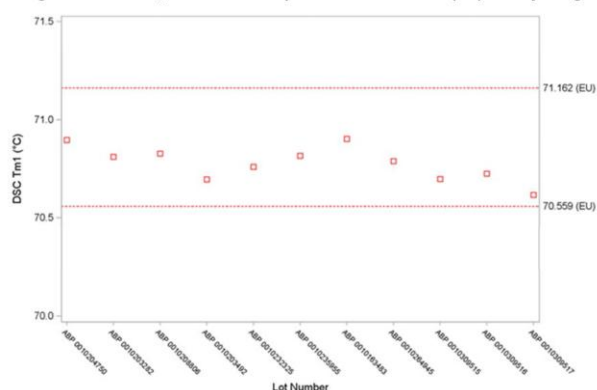


Figure 21. DSC T_{m2} - ABP 980 Compared to Trastuzumab (EU) Quality Range

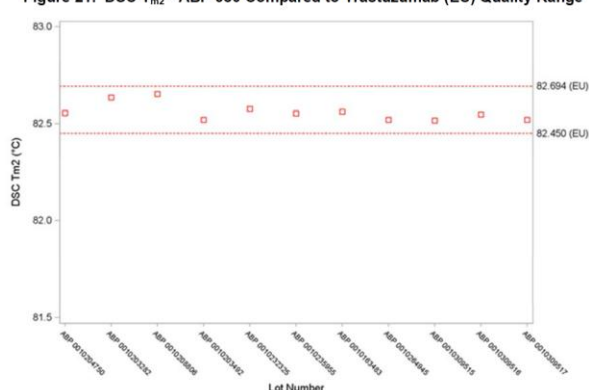


Figure 22. DSC T_{m1} - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range

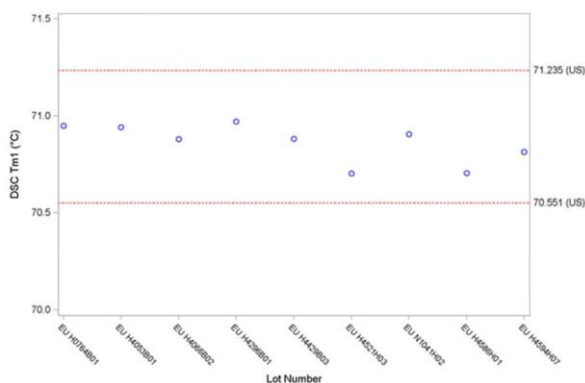
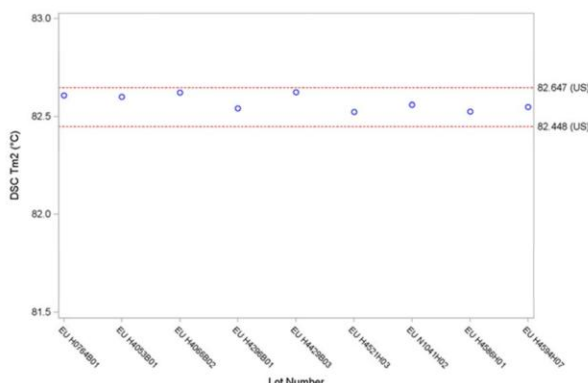


Figure 23. DSC T_{m2} - Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: As with FTIR and CD, the DSC data sets provided by the applicant, both the reference comparison and the spectral overlay, support similar higher-order structures between ABP 980 US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.3 Product-Related Substances and Impurities

Product-related substances and impurities of ABP 980, US-licensed Herceptin and EU-approved Herceptin were assessed, as follows:

- Size variants were assessed by size exclusion ultra-high performance liquid chromatography (SE-UHPLC), reduced capillary electrophoresis-sodium dodecyl sulfate (rCE-SDS), and non-reduced capillary electrophoresis-sodium dodecyl sulfate (nrCE-SDS)
- Charge variants were assessed by cation exchange high performance liquid chromatography (CEX-HPLC).

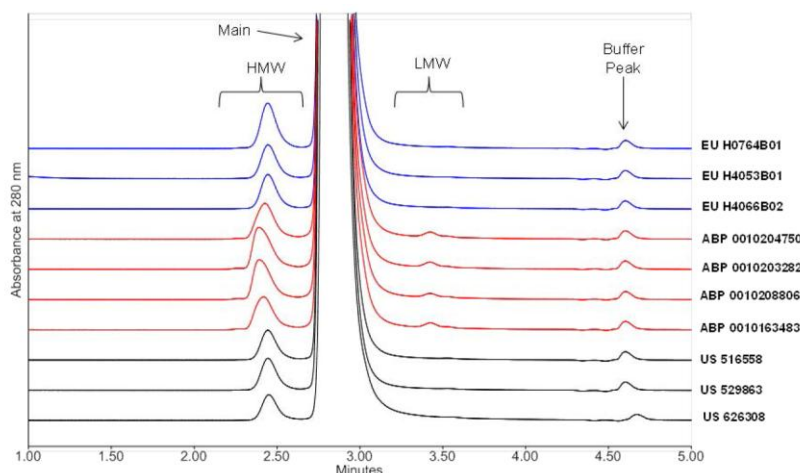
13 ABP 980 lots, 21 US-licensed Herceptin lots, and 33 EU-approved Herceptin lots were analyzed by each assay above. The 13 ABP 980 lots were produced from independent DS lots, including clinical and commercial lots.

3.2.R.1.3.1 Size Exclusion Ultra-high Performance Liquid Chromatography (13:21:33)

Reviewer Comment: The SE-UHPLC assay is proposed for use as a routine release test. Assay validation is presented in section 3.2.S.4.3.

For similarity assessment, SE-UHPLC profile and % LMW were analyzed using Tier 3 descriptive statisticals, while % HMW and main peak were analyzed using Tier 2 quality range statistics. The Tier 2 method applied two different quality ranges, defined as the Mean $\pm$ 3xSD of US-licensed Herceptin lots (21) or EU-approved Herceptin lots (33), respectively.

The SE-UHPLC profiles are visually similar among the three products with no new or missing peaks observed for ABP 980. A representative chromatogram of the SE-HPLC profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots is provided below. Although the levels of LMW in ABP 980 ($\leq 0.3\%$) are slightly higher than those in US-licensed Herceptin or EU-approved Herceptin ($\leq$ LOQ, 0.1%), the overall levels are very low and do not have a meaningful impact on the biological behavior of the molecule.



The results of HMW and main peak for ABP 980 lots against independent quality ranges of US-licensed Herceptin and EU-approved Herceptin, are provided in the following Figures. Additionally, each EU-approved Herceptin lot was assessed against the quality ranges of US-licensed Herceptin. One ABP 980

lot fell outside of the quality range of EU-approved Herceptin for main peak by 0.1% of the quality range lower limit (see Figure 95 below). However, the rest of results for HMW and main peak are within the respective quality ranges resulting in >90% of the ABP 980 lots testing within the quality range limits.

Figure 92. SE-UHPLC HMW - ABP 980 First Time Point Values Compared to Trastuzumab (US) First Time Point Quality Range

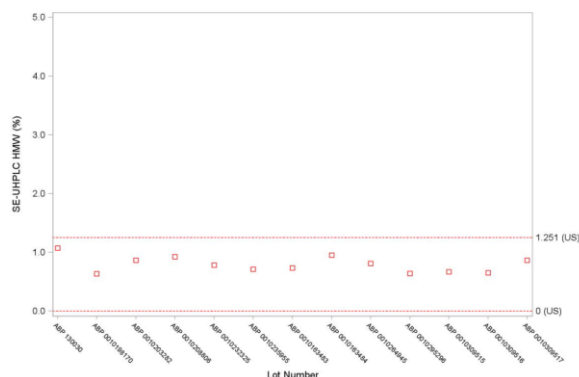


Figure 93. SE-UHPLC Main Peak - ABP 980 First Time Point Values Compared to Trastuzumab (US) First Time Point Quality Range

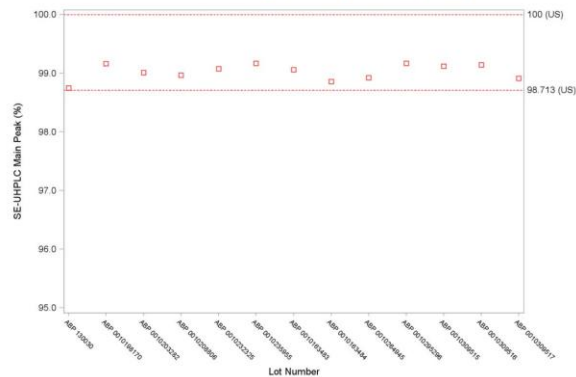


Figure 94. SE-UHPLC HMW - ABP 980 First Time Point Values Compared to Trastuzumab (EU) First Time Point Quality Range

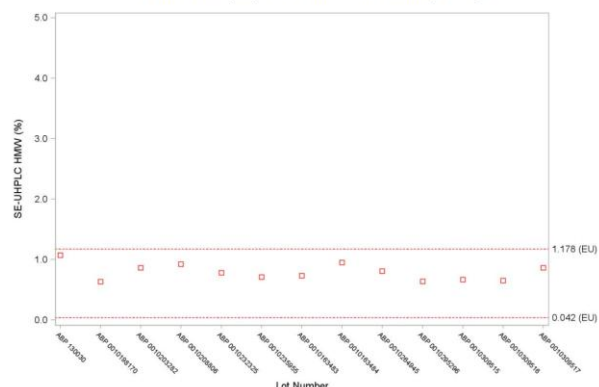


Figure 95. SE-UHPLC Main Peak - ABP 980 First Time Point Values Compared to Trastuzumab (EU) First Time Point Quality Range

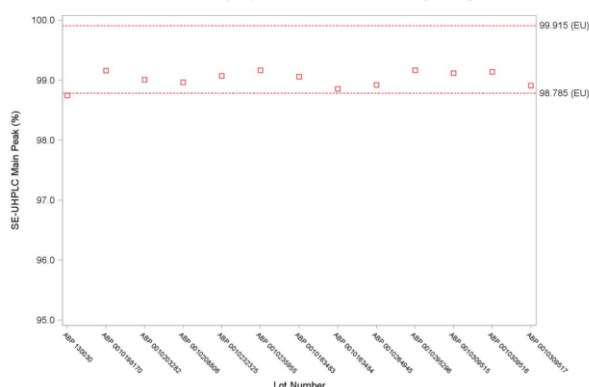


Figure 96. SE-UHPLC HMW - Trastuzumab (EU) First Time Point Values Compared to Trastuzumab (US) First Time Point Quality Range

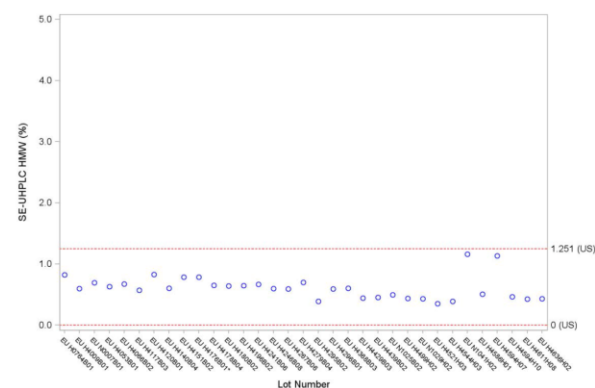
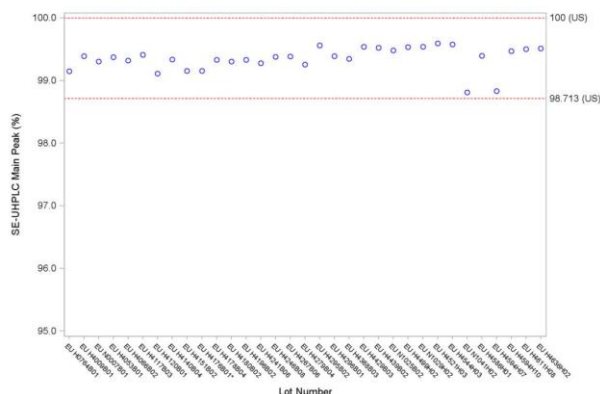


Figure 97. SE-UHPLC Main Peak - Trastuzumab (EU) First Time Point Values Compared to Trastuzumab (US) First Time Point Quality Range



Reviewer Comment: The small difference in main peak observed between ABP and EU-approved Herceptin is not expected to have a meaningful impact on the biological behavior of the molecule.

The levels of HMW and main peak change over time during storage at the recommended storage temperature. Thus, the results of HMW and main peak for each lot tested were age adjusted to their respective end of shelf life (36 months for ABP 980, 48 months for US-licensed Herceptin and EU-approved Herceptin), using a single linear regression model. For US-licensed Herceptin and EU-approved Herceptin lots, the age at the time of testing was calculated according to the lot expiry date and approved shelf life (48 month). For ABP 980 lots, the age of product was calculated based on the manufacturing date.

Reviewer Comment: *The linear regression analyses for product age adjustments are provided in Appendix 3 of the Product-related substances and impurities report. The model relies on calculation of product-specific slopes and estimates of the lot-specific intercept values to generate age-adjusted values for a common time point (i.e., final value = lot specific intercept + product specific intercept x time point). However, the potential for different combinations of attributes to influence rates of change over time introduces additional variables. The regression model and resulting age-adjusted values shown below are therefore only considered as supportive data for evaluation of stability-indicating attributes.*

The comparison for age adjusted results is provided below. Each ABP 980 lot was assessed against the Tier 2 quality ranges established based on age adjusted results for US-licensed Herceptin and EU-approved Herceptin. The results demonstrate that the level of % HMW estimated for ABP 980 at 36 months is similar US-Approved Herceptin at 48 months, and 11 of the 13 ABP 980 lots (85%) are within the main peak range.

Reviewer Comment: *Two ABP 980 lots have slight higher main peak levels that are within 0.1% of the US-licensed Herceptin quality range. It is not expected to have a meaningful impact on the biological behavior of the molecule.*

Figure 7. SE-UHPLC HMW - ABP 980 Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range

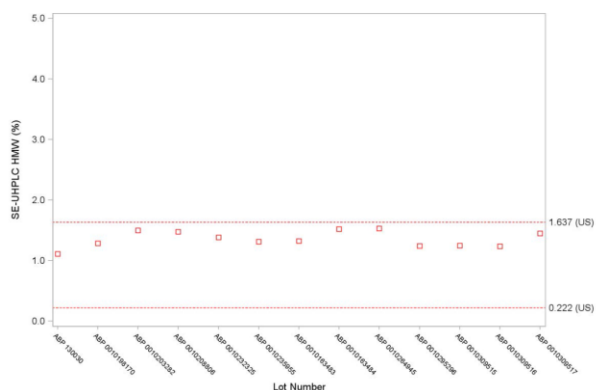
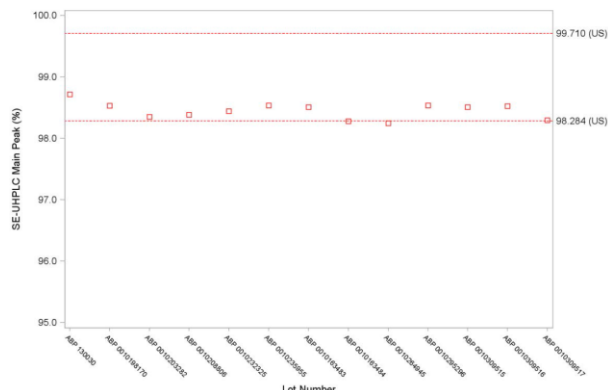


Figure 8. SE-UHPLC Main Peak – ABP 980 Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range



For comparison of ABP 980 and EU-approved Herceptin, the age-adjusted results showed that ABP 980 has slightly higher level of HMW and corresponding lower level for main peak compared to EU-approved Herceptin. In addition, all EU-approved Herceptin lots fall within the quality ranges of US-licensed Herceptin for HMW and main peak.

Reviewer Comment: These data suggest that although HMW species of ABP 980 lots are largely within the reference product quality range, they may occur at slightly higher levels on average in the ABP 980 lots. HMW species can impact biological activity, immunogenicity, or PK. The predominant HMW species in ABP 980 have been characterized as dimers. The potential slight differences in HMW species content between ABP 980 and US-licensed Herceptin is unlikely to impact biological behavior of the molecule for the following reasons: (1) biological characterization data on samples enriched with dimers support that these HMW species retain in vitro biological activity; and (2) the overall levels of HMW in the three products are low ($\leq 1.5\%$) and consistent with ranges typically observed for monoclonal antibodies. Therefore, the small differences in HMW and main peak observed do not preclude demonstration that ABP 980 is highly similar to US-licensed Herceptin.

Figure 9. SE-UHPLC HMW - ABP 980 Age-adjusted Values Compared to Trastuzumab (EU) Age-adjusted Quality Range

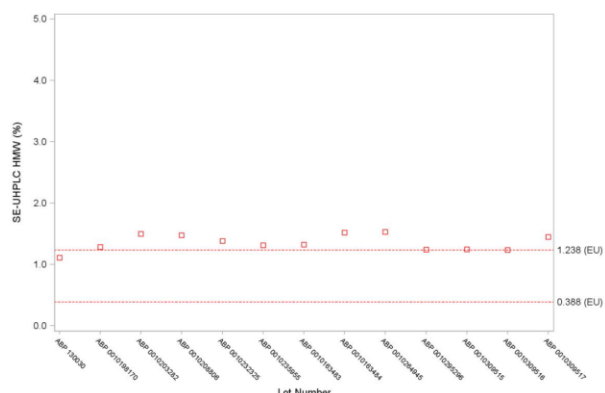


Figure 10. SE-UHPLC Main Peak - ABP 980 Age-adjusted Values Compared to Trastuzumab (EU) Age-adjusted Quality Range

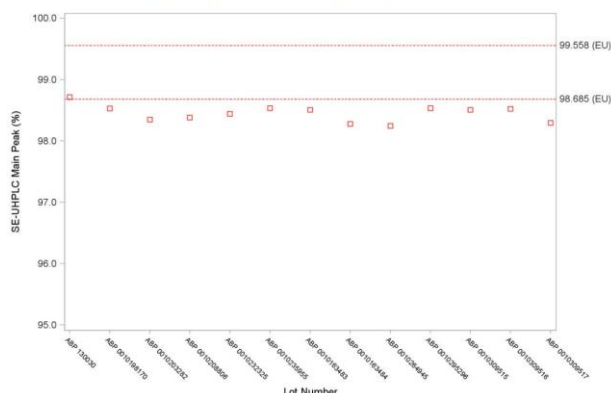


Figure 11. SE-UHPLC HMW - Trastuzumab (EU) Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range

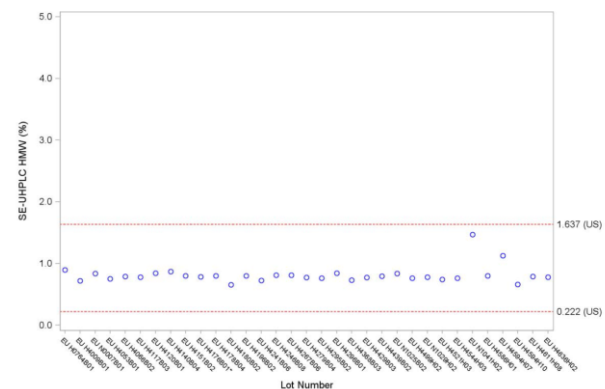
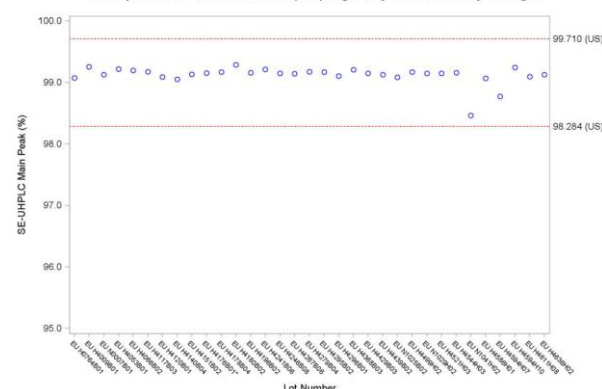


Figure 12. SE-UHPLC Main Peak - Trastuzumab (EU) Age-adjusted Values Compared to Trastuzumab (US) Age-adjusted Quality Range



Reviewer Comment: The data presented on size variants, both age-adjusted values as well as release data values, supports a determination of high similarity between ABP 980 and US-licensed Herceptin. Furthermore, data provided support the adequacy of the analytical bridge to support the use of EU-approved Herceptin in clinical studies.

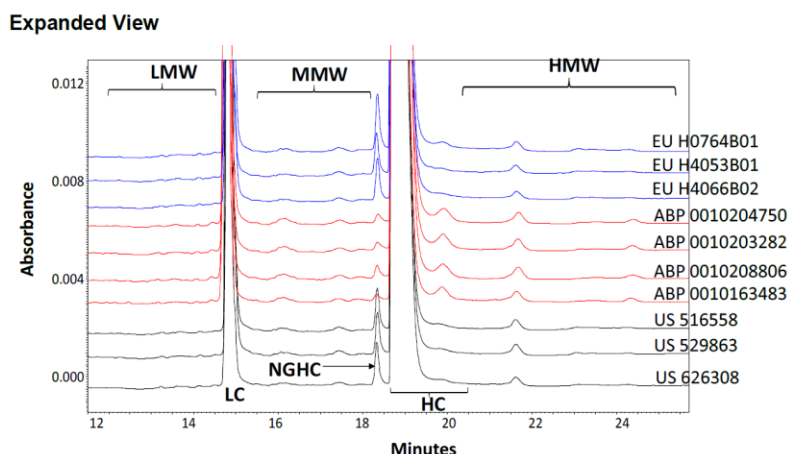
3.2.R.1.3.2 Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS) (13:21:33)

Reviewer Comment: This assay is proposed as a specification test, and assay validation is presented in section 3.2.S.4.3.

The similarity assessment was performed on

- rCE-SDS profile comparison, which was evaluated using a Tier 3 method
- rCE-SDS size variants, which were evaluated using a Tier 2 statistical method. Similarity assessment criteria for rCE-SDS were established on 3 groups: (1) purity (% HC + LC); (2) % NGHC; and (3) fragment % LMW + MMW, where:
 - HC: Heavy Chain
 - LC: Light Chain
 - NGHC: Non-Glycosylated Heavy Chain
 - LMW: Low Molecular Weight
 - MMW: Mid Molecular Weight Species

The independent quality ranges of US-licensed Herceptin and EU-approved Herceptin for rCE-SDS % HC+LC, NGHC, and LMW+MMW were established using the mean $\pm$ 3xSD of 33 US-licensed Herceptin lots and 21 EU-approved Herceptin lots, respectively. A representative comparison of rCE-SDS profile for the three products is provided below.



Reviewer Comment: The rCE-SDS profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin are visually similar, and no new species were observed for ABP 980. A higher level of post-HC peak in ABP 980 was detected compared to US-licensed Herceptin and EU-approved Herceptin. The post-HC peak is integrated as part of HC and has been identified as non-consensus glycosylation. According to literature, the non-consensus glycosylation also occurs in endogenous antibodies. Given the levels of post-HC peak are consistent and low ($\leq$ 1%) for ABP 980, it is not considered to impact biological behavior of the molecule. In addition, the rCE-SDS profiles for ABP 980 show lower levels of NGHC that are discussed below.

Comparison of rCE-SDS Tier 2 attributes between ABP 980 and US-licensed Herceptin, ABP 980 and EU-approved Herceptin, US-licensed Herceptin and EU-approved Herceptin, is presented below:

Figure 21. rCE-SDS HC + LC - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

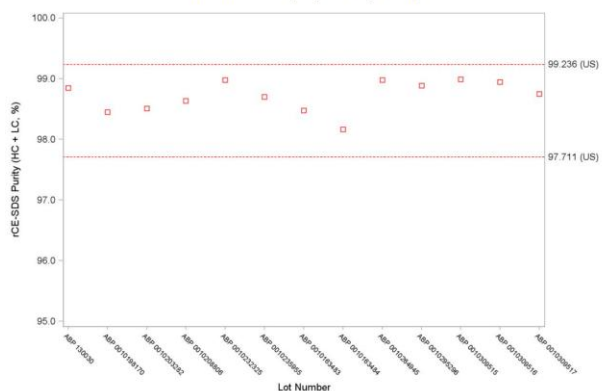


Figure 24. rCE-SDS HC + LC - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (EU) Quality Range

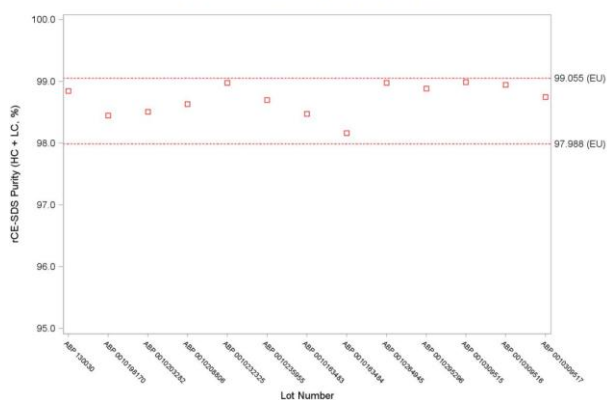


Figure 22. rCE-SDS LMW + MMW - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

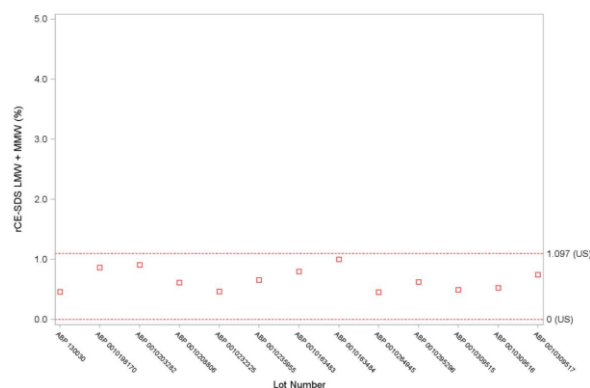


Figure 25. rCE-SDS LMW + MMW - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (EU) Quality Range

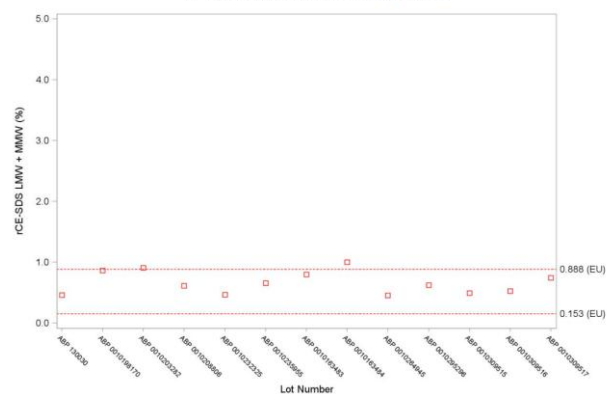


Figure 23. rCE-SDS NGHC - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

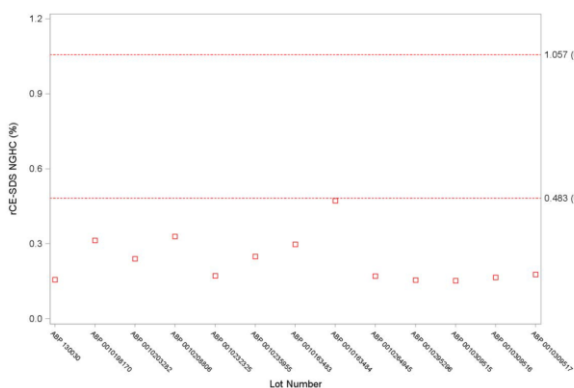


Figure 26. rCE-SDS NGHC - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (EU) Quality Range

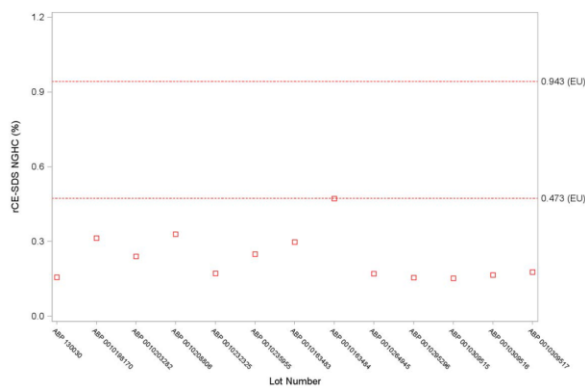


Figure 27. rCE-SDS HC + LC - Trastuzumab (EU) Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

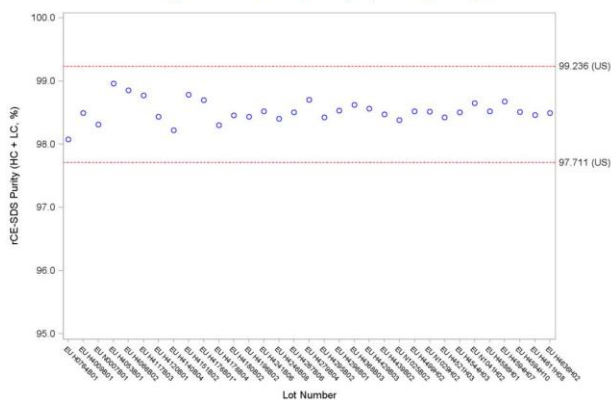


Figure 28. rCE-SDS LMW + MMW - Trastuzumab (EU) Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

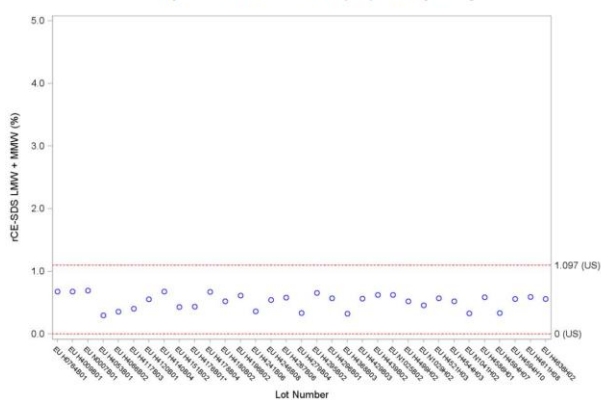
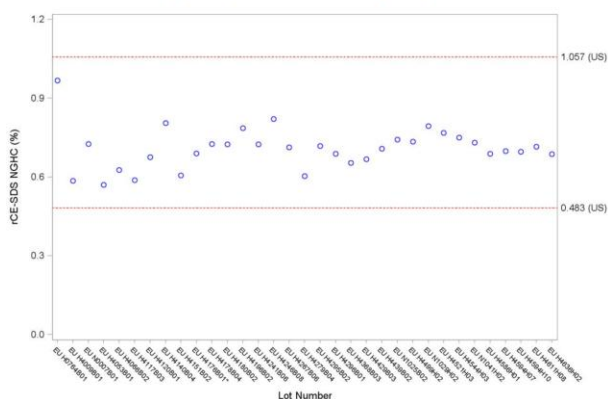


Figure 29. rCE-SDS NGHC - Trastuzumab (EU) Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range



Reviewer Comment: The following conclusions were drawn for comparison of Tier 2 attributes

- ABP 980, US-licensed Herceptin, and EU-approved Herceptin, are similar with respect to rCE-SDS purity (HC + LC). All of the ABP 980 lots are within the US-licensed Herceptin quality range and EU-approved Herceptin quality range.
- ABP 980, US-licensed Herceptin, and EU-approved Herceptin, are similar with respect to rCE-SDS fragments (LMW + MMW). Although results of rCE-SDS LMW + MMW for two ABP 980 lots are out of EU-approved Herceptin quality range, the differences observed are within 0.1% of the quality range. All ABP 980 lots and all EU-approved Herceptin lots tested within the US-licensed Herceptin quality range for fragments (LMW + MMW). Therefore, these data support the conclusion that ABP 980 is highly similar to the US licensed Herceptin and support the analytical bridge. The potential small difference between ABP 980 and EU-approved Herceptin is considered too small to preclude a finding of high similarity and the establishment of the analytical bridge.
- A lower level of % NGHC was observed for ABP 980 compared to US-licensed Herceptin, and EU-approved Herceptin. On average, the levels of % NGHC are ~0.5% lower in ABP 980 lots. However, the overall levels of NGHC in the three products are low ($\leq 1\%$). The minor quantitative differences observed are not expected to impact product biological activity. Additionally, the results from FcγRIIIa binding (refer to the section below) are similar among three products. Therefore, the difference observed does not preclude a determination that ABP 980 is highly similar to US-licensed Herceptin or the establishment of the analytical bridge.

- *US-licensed Herceptin, and EU-approved Herceptin, are similar with respect to rCE-SDS purity (HC + LC), fragments (LMW + MMW), and % NGHC.*

Taken together, data provided support a determination of high similarity between ABP 980 and US-licensed Herceptin, and the adequacy of the analytical bridge to support the use of EU-approved Herceptin in clinical study.

3.2.R.1.3.3 Non-reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (nrCE-SDS) (13:21:33)

For similarity assessment, nrCE-SDS size variants (% main peak; % pre-peaks) were classified as Tier 2 attributes. Each ABP 980 lot was compared against the quality ranges (Mean $\pm$ 3xSD) of US-licensed Herceptin and EU-approved Herceptin, respectively. A comparison of the nrCE-SDS profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots is provided below. The nrCE-SDS profile was assessed as a Tier 3 attribute.

Reviewer Comment: *The nrCE-SDS is proposed as a specification test, and assay validation is presented in section 3.2.S.4.3.*

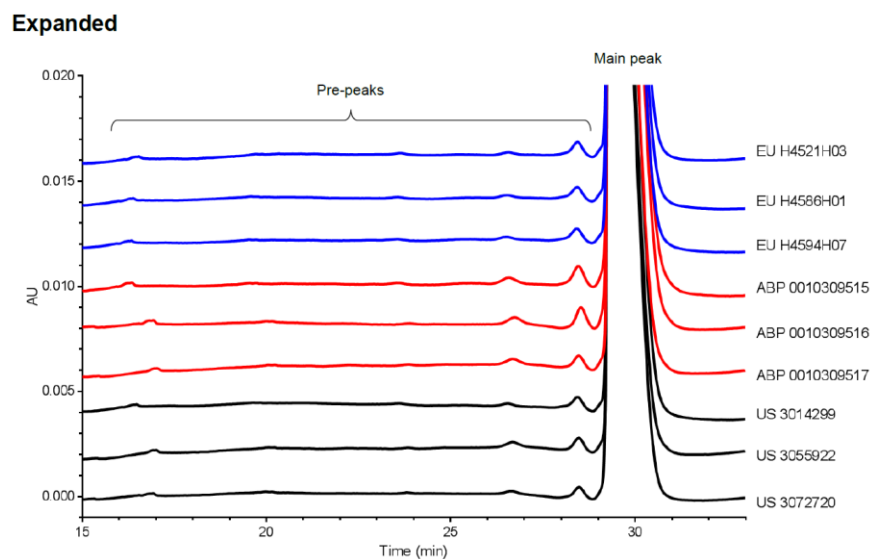


Figure 36. nrCE-SDS Main Peak - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

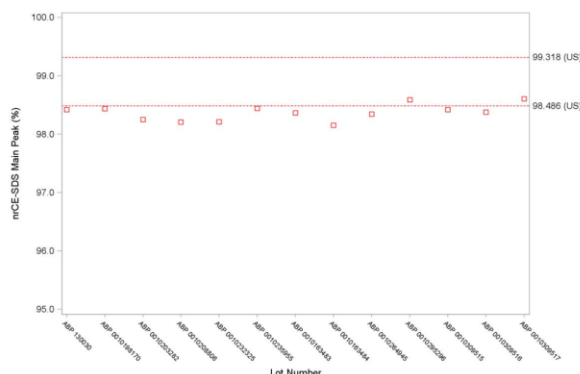


Figure 38. nrCE-SDS Main Peak - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (EU) Quality Range

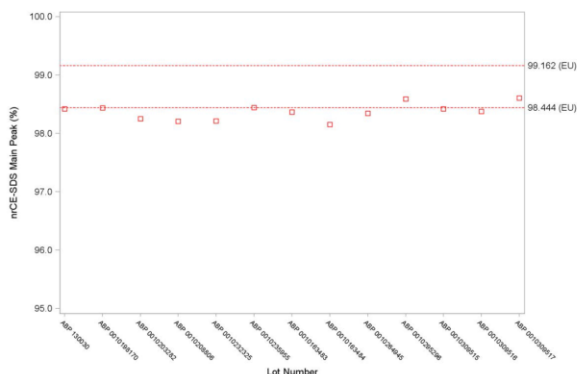


Figure 37. nrCE-SDS Pre-peaks - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

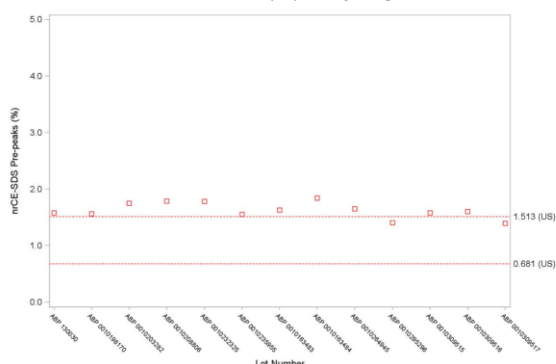


Figure 39. nrCE-SDS Pre-peaks - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (EU) Quality Range

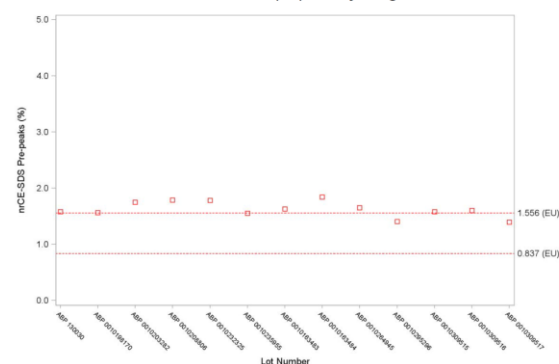


Figure 40. nrCE-SDS Main Peak - Trastuzumab (EU) Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

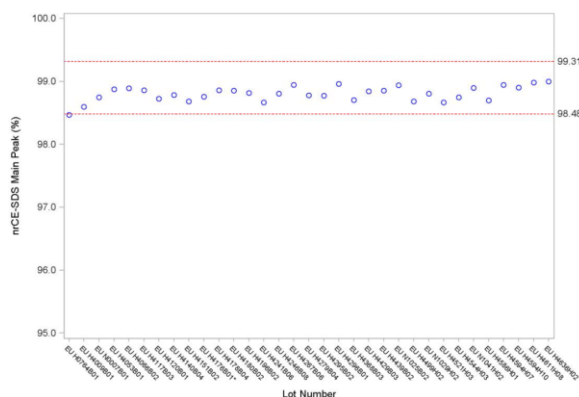
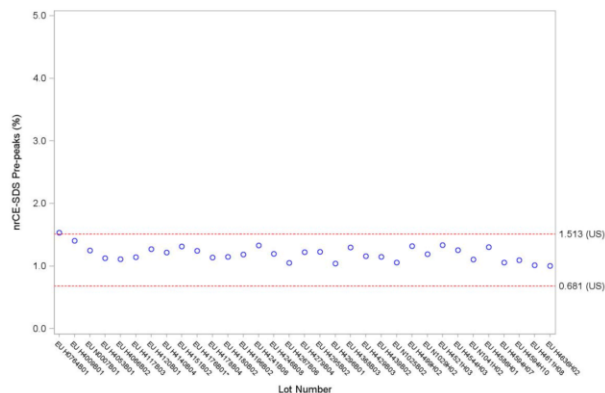


Figure 41. nrCE-SDS Pre-peaks - Trastuzumab (EU) Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range



Reviewer Comment: The following conclusions were drawn:

- The nrCE-SDS profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin are visually similar and no new species were observed for ABP 980. Expanded views of the nrCE-SDS profiles are provided in the submission that further support this conclusion.
- A higher level of pre-peaks and corresponding lower level of main peak was observed for ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin. The differences in main peak and pre-peaks are within 0.4% of the quality range limits of US-licensed Herceptin and EU-approved Herceptin. The pre-peak levels represent partially-reduced species with open

disulfide structures and clipped species. Such structural differences could impact function. However, the biological characterization data (cell proliferation and Fc effector assays) show no loss of function when compared to US-licensed and EU-approved Herceptin lots. Published literature support re-oxidation of mAb disulfide bonds in vivo, thus small differences in partially reduced species do not have a meaningful impact on the biological behavior of the molecule. Given the high purity for all products (98-99%), the equivalent potency results (see sections below), and known re-oxidations conditions in vivo, the residual uncertainty due to these minor differences are considered negligible and do not preclude a demonstration that ABP 980 is highly similar to US-licensed Herceptin.

- *US-licensed Herceptin, and EU-approved Herceptin, are similar with respect to nrCE-SDS main peak and pre-peaks.*

The data in concert with review of other functional assay data support a determination of similarity between ABP 980 and US-licensed Herceptin. Additionally, data provided support the adequacy of the analytical bridge.

3.2.R.1.3.4 Cation Exchange – High Performance Liquid Chromatography (CEX-HPLC) (13:21:33)

Reviewer Comment: *This assay is proposed as a specification test, and assay validation is presented in section 3.2.S.4.3.*

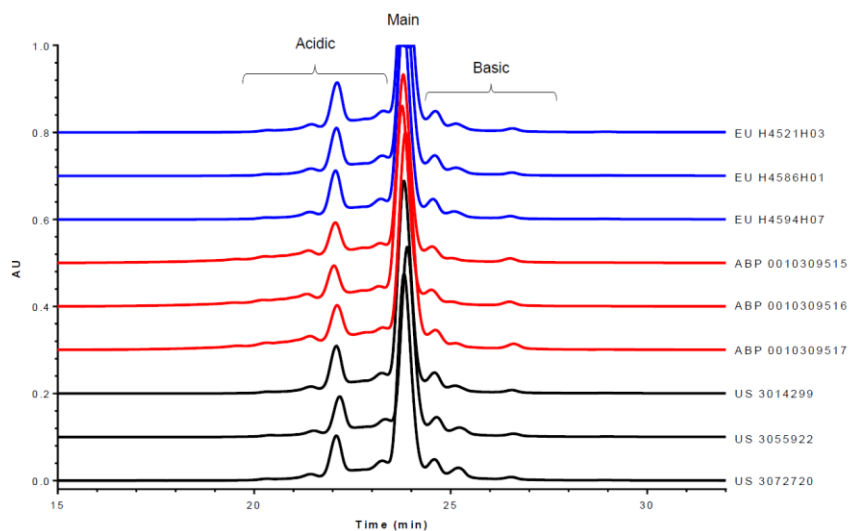
The similarity assessment was performed on

- CEX-HPLC profile comparison, which was evaluated using a Tier 3 method
- CEX-HPLC charge groups (acidic peaks, main peak, and basic peaks), which was evaluated using a Tier 2 statistical method. The similarity assessment criteria for each group were established based on quality ranges of US-licensed Herceptin or EU-approved Herceptin (Mean $\pm$ 3xSD).

A comparison of the CEX-HPLC profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots is provided below.

Reviewer Comment: *The CEX-HPLC profiles are similar across the 3 products with no new or missing peaks observed.*

Expanded View



A comparison of the CEX-HPLC charge variants for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots is provided below.

Acidic peaks

Relatively higher levels of acidic peaks were observed in ABP 980 lots compared to US-licensed Herceptin and EU-approved Herceptin lots, while all EU-approved Herceptin lots fall within US-licensed Herceptin quality range.

Figure 50. CEX-HPLC Acidic Peaks - ABP 980 Non-age Adjusted Results Compared to Trastuzumab (US) Quality Range

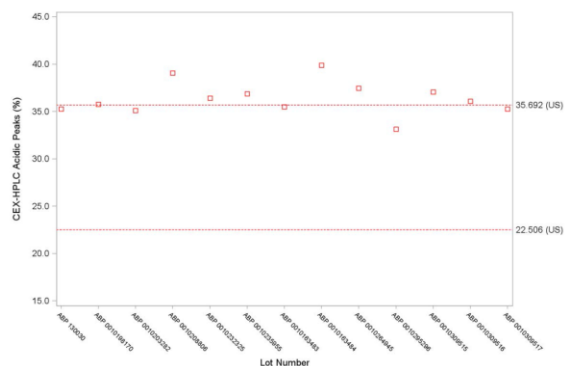
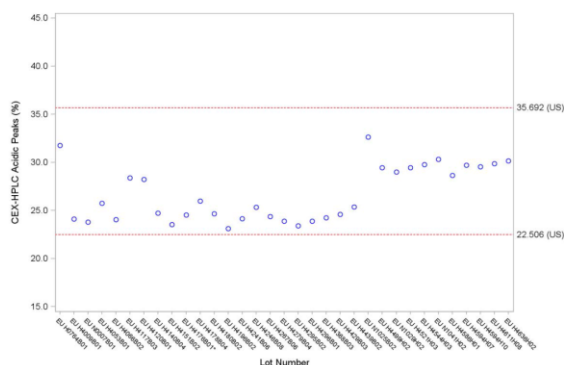


Figure 56. CEX-HPLC Acidic Peaks - Trastuzumab (EU) Values Compared to Trastuzumab (US) Quality Range



Reviewer Comment: These data show ~5-10% higher levels of acidic variants in ABP 980 lots. Each fraction of acidic variants was enriched from ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots and characterized with respect to asparagine deamidation, methionine oxidation, glycosylation patterns, size variants, and biological activities (proliferation inhibition and ADCC). Characterization data for acidic fractions are shown below. Overall similar distribution of post-translational modification was observed across the three products. The difference in acidic peaks for ABP 980 relative to US-licensed Herceptin, and EU-approved Herceptin is predominantly attributed to non-consensus glycosylation and partially reduced species. Additionally, each fraction of acidic species has similar biological activity among the three products.

Table 11. Key Modifications in the Enriched Acidic Variants Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	ABP 980 (%)					Trastuzumab (US) (%)					Trastuzumab (EU) (%)				
	N ^{55a}	N ^{30b}	M ^{255c}	M ^{431d}	M ^{107e}	N ^{55a}	N ^{30b}	M ^{255c}	M ^{431d}	M ^{107e}	N ^{55a}	N ^{30b}	M ^{255c}	M ^{431d}	M ^{107e}
Starting material	2	12	3	2	1	2	16	2	1	1	3	13	2	1	1
A1-1	10	35	13	11	7	8	40	14	11	6	9	37	13	10	8
A1-2	7	34	9	8	5	7	45	9	7	5	7	41	9	8	6
A1-3	7	21	5	6	3	7	27	6	5	3	7	23	6	5	3
A2	1	31	5	5	3	2	39	4	3	2	3	35	4	3	2
A3-1	1	13	6	6	3	2	19	5	4	2	3	17	5	4	3
A3-2	1	8	5	5	3	2	12	5	3	2	3	11	4	3	3
Main	1	6	4	3	2	2	9	3	2	1	3	9	3	2	2

^a Heavy chain N⁵⁵ deamidation (%)

^b Light chain N³⁰ deamidation (%)

^c Heavy chain M²⁵⁵ oxidation (%)

^d Heavy chain M⁴³¹ oxidation (%)

^e Heavy chain M¹⁰⁷ oxidation (%)

Table 12. Glycan Analysis of the Enriched Acidic Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	ABP 980 (%)				Trastuzumab (US) (%)				Trastuzumab (EU) (%)			
	Afuco-sylated	Galacto-sylated	High Mannose	Sialy-lated	Afuco-sylated	Galacto-sylated	High Mannose	Sialy-lated	Afuco-sylated	Galacto-sylated	High Mannose	Sialy-lated
Starting material	8.5	49.1	2.0	1.3	7.4	41.5	2.5	1.8	8.2	41.9	2.7	1.9
A1-1	7.7	54.6	2.1	1.9	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a
A1-2	7.7	53.4	2.3	1.7	7.0	46.6	2.2	2.7	7.2	48.2	2.4	3.3
A1-3	7.9	51.6	2.3	1.9	6.5	45.6	2.5	3.3	7.5	45.7	2.7	3.6
A2	8.1	50.6	2.2	1.2	6.9	43.0	2.2	1.4	7.9	44.0	2.5	1.5
A3-1	8.6	50.0	2.3	2.0	6.9	44.5	2.3	3.3	7.8	45.3	2.7	3.8
A3-2	7.8	51.8	2.4	3.8	6.7	45.4	2.8	5.7	7.2	46.8	3.3	6.9
Main	9.0	46.7	2.1	0.7	7.9	39.4	2.5	0.8	8.7	39.5	2.8	0.9

^a Fraction was not tested due to low abundance and insufficient amount of available material

Table 14. rCE-SDS Results of Enriched Acidic Charge Variant Fractions for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

	Trastuzumab (EU) (%)						ABP 980 (%)						Trastuzumab (US) (%)					
	LMW	LC	MMW	NGHC	HC	HMW	LMW	LC	MMW	NGHC	HC	HMW	LMW	LC	MMW	NGHC	HC	HMW
Starting material	0.1	30.7	0.4	0.6	67.9	0.3	0.0	30.9	0.4	0.2	67.9	0.5	0.2	30.5	0.4	0.7	67.9	0.3
A1-1	N/A ^a						0.1	30.3	1.2	0.5	65.8	1.9	N/A ^a					
A1-2	0.0	30.6	0.8	0.7	66.8	1.1	0.1	30.7	0.5	0.3	67.0	1.3	0.2	30.2	0.8	0.7	67.0	1.1
A1-3	0.2	30.6	0.4	0.7	67.6	0.6	0.0	30.5	0.4	0.2	67.8	0.9	0.2	30.2	0.3	0.7	67.8	0.8
A2	0.0	30.6	0.4	0.7	68.0	0.4	0.1	30.5	0.3	0.1	68.4	0.5	0.1	30.3	0.3	0.7	68.1	0.5
A3-1	0.0	30.7	0.4	0.6	67.7	0.6	0.1	30.6	0.4	0.1	67.7	0.9	0.0	30.3	0.4	0.7	67.9	0.7
A3-2	0.0	30.6	0.4	0.7	67.8	0.5	0.0	30.4	0.4	0.2	68.3	0.5	0.2	30.2	0.5	0.7	67.8	0.6
Main	0.0	30.6	0.3	0.6	68.4	0.2	0.1	30.5	0.3	0.1	68.7	0.3	0.1	30.2	0.3	0.6	68.5	0.3

HC = heavy chain (includes post-HC peak); HMW = high molecular weight; LC = light chain; LMW = low molecular weight; MMW = middle molecular weight; NGHC = non-glycosylated heavy chain

^a Fraction was not tested due to low abundance and insufficient amount of available material.

Table 16. Relative Potency of Enriched Acidic Variants Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	ABP 980 (%)		Trastuzumab (US) (%)		Trastuzumab (EU) (%)	
	Relative Potency	Standard Deviation	Relative Potency	Standard Deviation	Relative Potency	Standard Deviation
Starting material	104	4	120	11	104	1
A1 ^a	86	11	81	15	116	3
A2	117	8	112	10	111	7
A3 ^a	94	8	87	22	97	3
Main	140	11	131	13	141	7

^a A1 represents combined A1-1, A1-2, and A1-3; A3 represents combined A3-1 and A3-2 fractions.

Table 17. Relative ADCC Activity of Enriched Acidic Variants Fractions for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

	Trastuzumab (EU) (%)		ABP 980 (%)		Trastuzumab (US) (%)	
	Relative Activity ^a	Standard Deviation	Relative Activity ^a	Standard Deviation	Relative Activity ^a	Standard Deviation
Starting material	89	14	85	6	99	10
A1-1	64	16	53	16	53	7
A1-2	76	12	59	4	61	2
A2	94	25	80	4	76	7
Main	100	11	100	28	100	7

^a Results are normalized to main peak

Main peak

Six of the 13 ABP 980 lots (46%) fall below the US-licensed Herceptin quality range, while 5 of the 13 ABP 980 lots (38%) fall below the EU-approved Herceptin quality range, indicating a lower level of main peak in ABP 980, relative to US-licensed Herceptin and EU-approved Herceptin. The difference in main peak is primarily due to the higher levels of acidic peaks in ABP 980. US-licensed Herceptin and EU-approved Herceptin lots are similar for the level of main peak.

Figure 100. CEX-HPLC Main Peak - ABP 980 First Timepoint Compared to Trastuzumab (US) First Time Point Quality Range

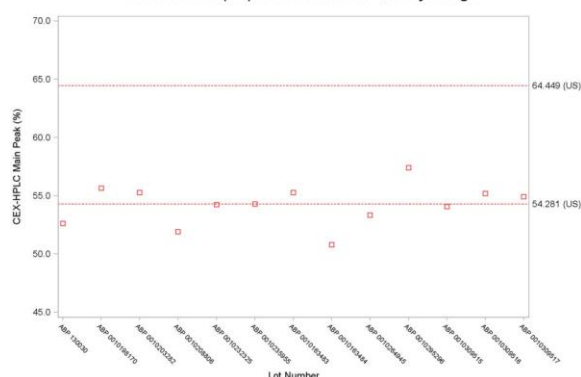


Figure 102. CEX-HPLC Main Peak - ABP 980 First Time Point Compared to Trastuzumab (EU) First Time Point Quality Range

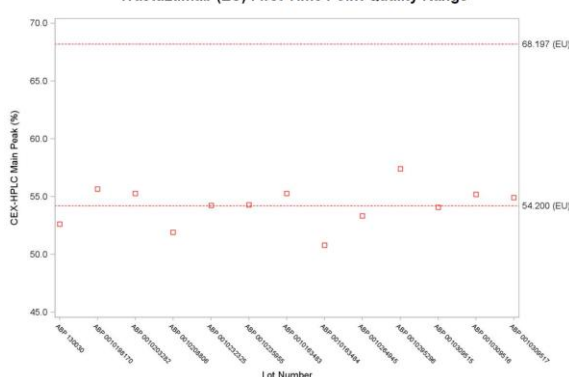
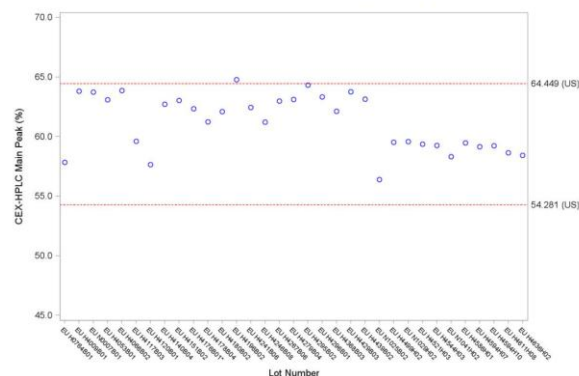


Figure 104. CEX-HPLC Main Peak - Trastuzumab (EU) First Time Point Compared to Trastuzumab (US) First Time Point Quality Range



Reviewer Comment: Results from the age adjustment set (36 months for ABP 980, 48 months for US-licensed Herceptin and EU-approved Herceptin) are provided and show similar results for main peak among the three products. Those data are not reproduced here.

Basic peaks

All ABP 980 lots fall within the US-licensed Herceptin range, indicating that the two products are similar with regard to CEX-HPLC basic peaks. Seven of the 13 ABP 980 lots (54%) fall below the EU-approved Herceptin quality range. Characterization of primary structure has shown that EU-approved Herceptin contains around 1% C-terminal lysine which is not present in ABP 980. The difference in C-terminal lysine may result in a relatively lower level of basic peaks in ABP 980. EU-approved Herceptin lots were compared to the US-licensed Herceptin for basic peaks. All lots tested fall within the US-licensed Herceptin range.

Figure 101. CEX-HPLC Basic Peaks - ABP 980 First Time Point Compared to Trastuzumab (US) First Time Point Quality Range

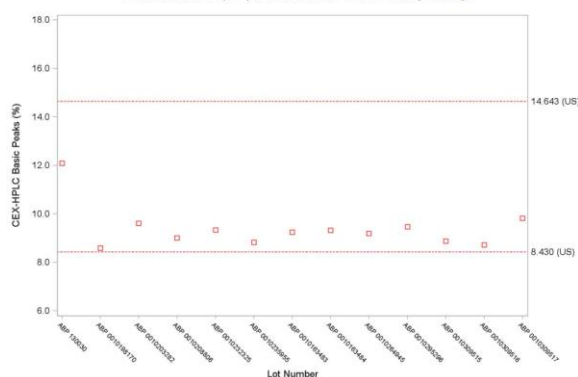


Figure 103. CEX-HPLC Basic Peaks - ABP 980 First Time Point Compared to Trastuzumab (EU) First Time Point Quality Range

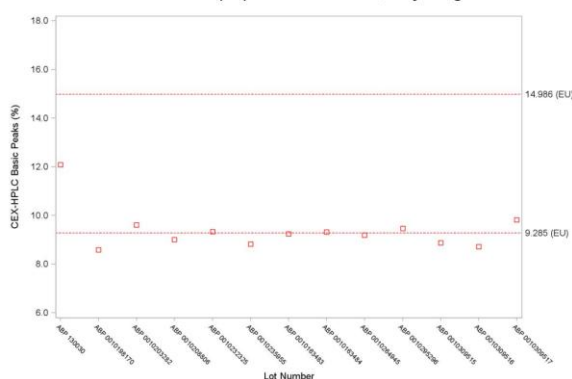
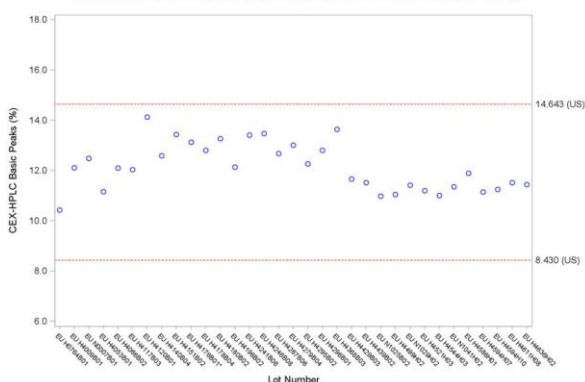


Figure 105. CEX-HPLC Basic Peaks - Trastuzumab (EU) First Time Point Compared to Trastuzumab (US) First Time Point Quality Range



Reviewer Comment: Each fraction of basic variants was purified and characterized for ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Overall similar distribution of post-translational modifications was observed in each fraction of basic variants across the three products, including aspartic acid isomerization, methionine oxidation, HMW species. US-licensed Herceptin and EU-approved Herceptin have around 1% C-terminal lysine which is not present in ABP 980. A slightly higher Fc oxidation trend (about 2% to 5%) is observed in ABP 980 as compared to US-licensed

Herceptin and EU-approved Herceptin. The differences in C-terminal lysine and Fc oxidation are not expected to be of biological significance here. Additionally, each fraction of basic peaks has similar biological activity among the three products.

Results from the age adjustment set (36 months for ABP 980, 48 months for US-licensed Herceptin and EU-approved Herceptin) are provided. All ABP 980 lots fall within the US-licensed Herceptin and EU-approved Herceptin ranges. Those data are not reproduced here.

Table 18. Key Modifications in Enriched Basic Variants Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	ABP 980 (%)					Trastuzumab (US) (%)					Trastuzumab (EU) (%)				
	D ^{102a}	M ^{255b}	M ^{431c}	M ^{107d}	C- K ^e	D ^{102a}	M ^{255b}	M ^{431c}	M ^{107d}	C- K ^e	D ^{102a}	M ^{255b}	M ^{431c}	M ^{107d}	C- K ^e
Starting material	4	3	2	1	0	7	2	1	1	1	6	2	1	1	1
Main	3	4	3	2	0	4	3	2	1	0	3	3	2	2	0
B1	30	8	8	4	0	34	5	4	2	3	30	5	4	3	4
B2	22	13	11	6	0	24	8	7	4	8	19	8	6	4	7
B3	23	10	9	4	0	25	8	6	4	1	23	7	5	3	2

^a Heavy chain D¹⁰² isomerization

^b Heavy chain M²⁵⁵ oxidation

^c Heavy chain M⁴³¹ oxidation

^d Heavy chain M¹⁰⁷ oxidation

^e Heavy chain C-terminal Lys

Table 22. nrCE-SDS Results of Enriched Basic Charge Variant Fractions for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

	Trastuzumab (EU) (%)			ABP 980 (%)			Trastuzumab (US) (%)		
	Pre-peaks	Main Peak	Post-peaks	Pre-peaks	Main Peak	Post-peaks	Pre-peaks	Main Peak	Post-peaks
Starting material	1.3	98.6	0.2	1.8	98.1	0.1	1.1	98.9	0.1
B1	2.7	97.0	0.3	3.4	95.9	0.7	1.9	97.9	0.3
B3	3.3	80.8	15.9	3.7	91.9	4.4	1.9	80.8	17.3
Main	0.8	99.1	0.1	0.5	99.3	0.1	0.3	99.7	0.1

Table 23. Relative Potency of Enriched Basic Variants Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	ABP 980 (%)		Trastuzumab (EU) (%)		Trastuzumab (US) (%)	
	Relative Potency	Standard Deviation	Relative Potency	Standard Deviation	Relative Potency	Standard Deviation
Starting material	104	4	104	1	120	11
Main	141	7	140	11	131	13
B1	14 ^a	21	11 ^a	26	9 ^a	18

^a Value is outside of validated range, shown for trending purposes only

Table 24. Relative ADCC Activity of Enriched Basic Variants Fractions for ABP 980, Trastuzumab (US), and Trastuzumab (EU)

	Trastuzumab (EU) (%)		ABP 980 (%)		Trastuzumab (US) (%)	
	Relative Activity ^a	Standard Deviation	Relative Activity ^a	Standard Deviation	Relative Activity ^a	Standard Deviation
Starting material	89	14	85	6	99	10
Main	100	11	100	28	100	7
B1 ^b	105	23	109	7	103	6

^a Results are normalized to main peak

Reviewer Comments: *The differences observed in the charge variant are not considered to preclude a determination of high similarity between ABP 980 and US-licensed Herceptin or the establishment of the analytical bridge, based on the following observations:*

- *The charge variants have been characterized for ABP 980, US-licensed Herceptin, and EU-approved Herceptin (refer to section Appendix 1). Data provided demonstrate similar distribution of post-translational modifications in each charge variants group across the three products.*
- *The potency of each fraction in the charge profile is similar among the three products.*
- *Additionally, the charge modifications for the acidic variant occur predominantly via deamidation of asparines that are not located in a region expected to influence PK.*
- *Similar FcRn binding were observed between the three products*
- *Similar functional assay results were observed between the three products.*

The data, in concert with review of other functional assay data, support a determination of high similarity between ABP 980 and US-licensed Herceptin. Additionally, the data provided support the adequacy of the analytical bridge.

3.2.R.1.4 Particles and Aggregates

Particle and aggregate profiles of ABP 980, US-licensed Herceptin, and EU-approved Herceptin were assessed as follows:

- Subvisible particles were evaluated quantitatively by light obscuration (HIAC) and microflow imaging (MFI)
- Submicron particles were evaluated qualitatively by field flow fractionation (FFF) and dynamic light scattering (DLS)
- Solution-state aggregates were assessed by analytical ultracentrifugation sedimentation velocity (AUC-SV)
- Characterization of the oligomers separated by size-exclusion HPLC was performed by light scattering detection (SE-HPLC-LS) to provide the approximate molar mass

3.2.R.1.4.1 Subvisible Particles

The levels of subvisible particles were determined as follows:

- The HIAC method measures $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$
- The MFI method was used to differentiate between spherical and non-spherical particles

Reviewer Comment: Data collected using the HIAC method were evaluated using Tier 3 criteria, and data collected using MFI were evaluated using both Tier 3 and Tier 2 criteria. Both methods are appropriate for their intended use in the similarity assessment.

3.2.R.1.4.1.1 HIAC Method (30:6:6)

The HIAC method was performed on 30 lots of ABP 980 and 6 lots each of US-licensed Herceptin and EU-approved Herceptin. The figures below provide comparison of the $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ subvisible particles.

Figure 1. HIAC $\geq 2 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

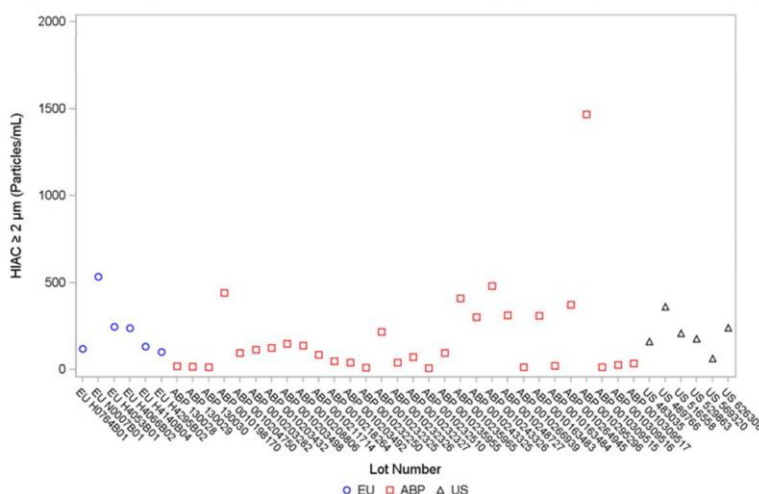


Figure 2. HIAC $\geq 5 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

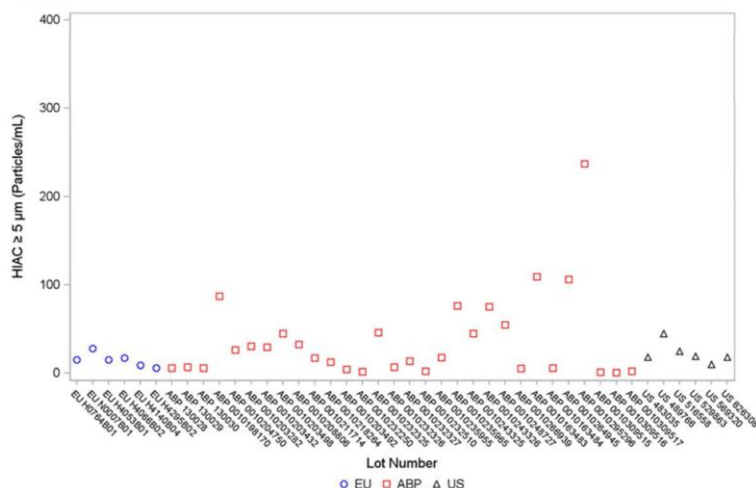


Figure 3. HIAC $\geq 10 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

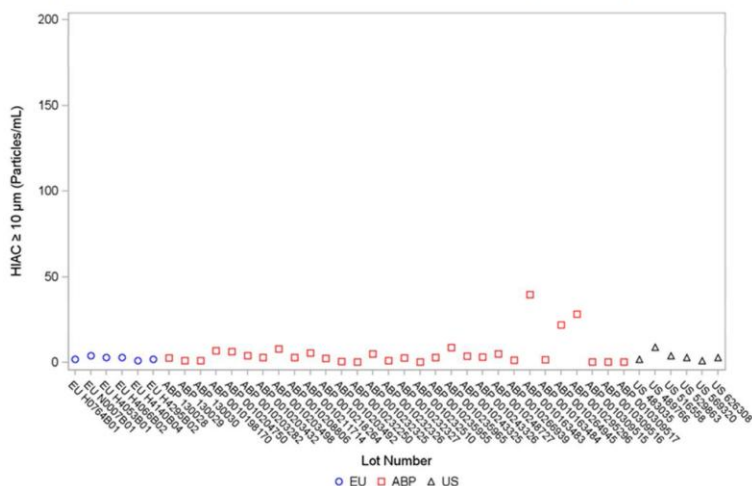
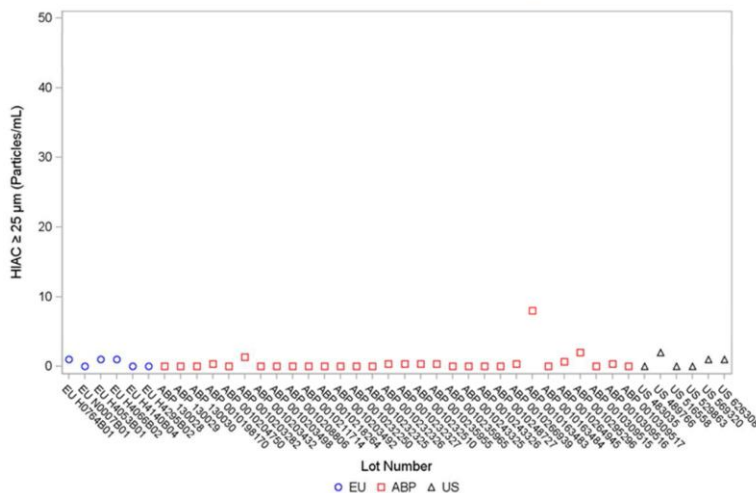


Figure 4. HIAC $\geq 25 \mu\text{m}$ Subvisible Particles Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The levels of sub-visible particles are influenced by the drug product manufacturing process. All ABP 980 clinical DP lots produced were included in similarity assessment except for lot 11E19WA, which was produced in Merck Sharp and Dohme (MSD) and used in early clinical study. For particles of $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$, although relatively higher levels of sub-visible particles were detected in a few ABP 980 lots (ABP 0010163483, ABP 0010264945, and ABP 0010295296 for particles $\geq 10 \mu\text{m}$; and ABP 0010163483 for particles $\geq 25 \mu\text{m}$), the differences may be attributable to high method variability and sample size. Overall, similar levels were observed in all lots of three products tested. The levels of particles (≥ 10 and ≥ 25) in three products are well within the limits of USP and PhEur. Regarding particles of $\geq 5 \mu\text{m}$, ABP 980 has relatively higher levels compared to US-licensed Herceptin and EU-approved Herceptin. For particles of $\geq 2 \mu\text{m}$, similar levels were observed in ABP 980 lots compared to US-licensed Herceptin and EU-approved Herceptin lots with exception of ABP 0010295296. The overall levels of particles of $\geq 5 \mu\text{m}$ and $\geq 2 \mu\text{m}$ are low. The difference observed would not have an adverse impact on safety. Additionally, similar results were obtained for all size particles between US-licensed Herceptin and EU-approved Herceptin. Overall, data support the conclusion that the three products have similar levels of sub-visible particles across all size ranges.

3.2.R.1.4.1.2 MFI Method (28:6:6)

The MFI method was performed on 20 lots of ABP 980 and 6 lots each of US-licensed Herceptin and EU-approved Herceptin. The sponsor states that two ABP 980 lots were not tested for MFI due to sample limitations. Cumulative particle counts for $\geq 5 \mu\text{m}$ particles were reported. The MFI method is able to differentiate between spherical particles (silicon oil) and non-spherical particles (protein) in the $\geq 5 \mu\text{m}$ range. For similarity assessment, non-spherical particles are considered a Tier 2 attribute, as these are considered to have a higher biological relevance, whereas spherical particles are considered a Tier 3 attribute.

The figures below provide the $\geq 5 \mu\text{m}$ particles and $\geq 5 \mu\text{m}$ non-spherical subvisible particle results for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

Figure 5. MFI $\geq$ Total $5 \mu\text{m}$ Subvisible Particle Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

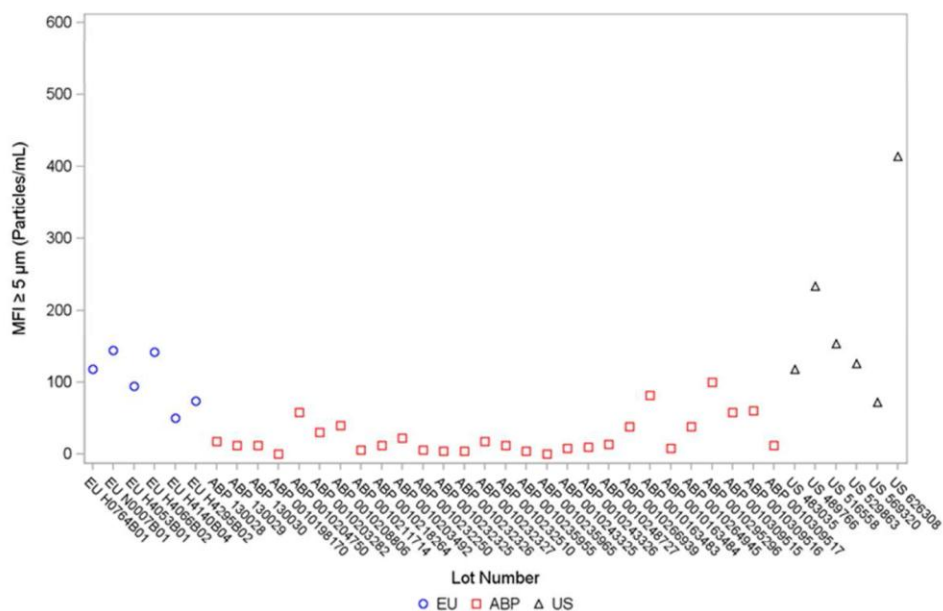
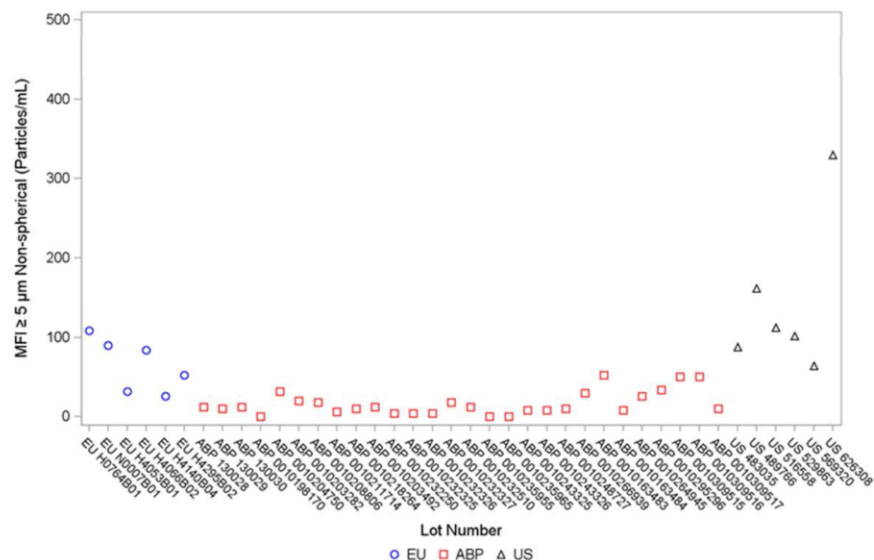


Figure 6. MFI $\geq 5 \mu\text{m}$ Non-spherical Subvisible Particle Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Each ABP 980 lot was compared against the 2 independent Tier 2 quality ranges (Mean $\pm$ 3xSD) established based on US-licensed Herceptin and EU-approved Herceptin as shown below. Additionally, each EU-approved Herceptin lot was assessed against the quality range established based on US-licensed Herceptin.

Figure 7. MFI $\geq$ 5 μ m Non-spherical Subvisible Particles - ABP 980 Compared to Trastuzumab (US) Quality Range

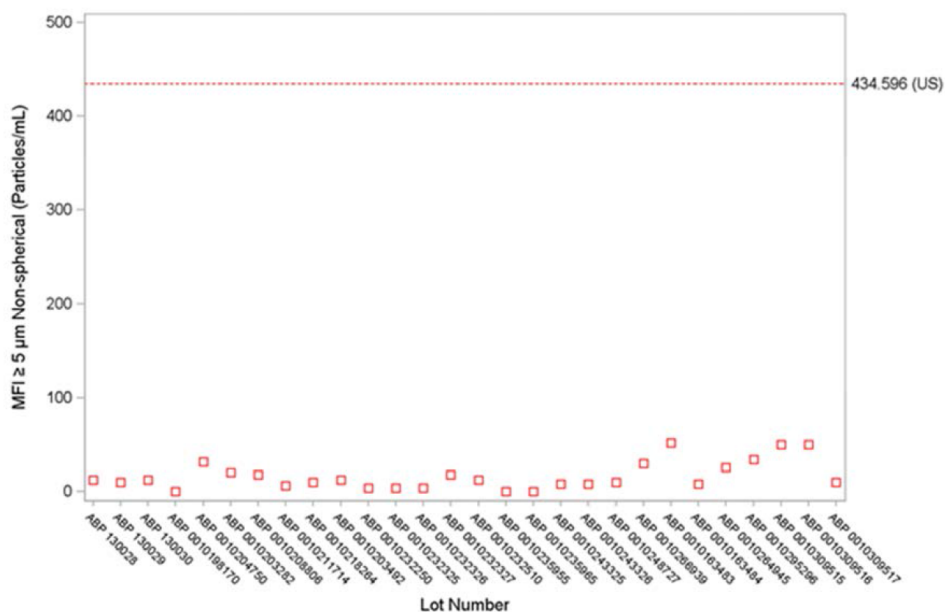


Figure 8. MFI $\geq$ 5 μ m Non-spherical Subvisible Particles - ABP 980 Compared to Trastuzumab (EU) Quality Range

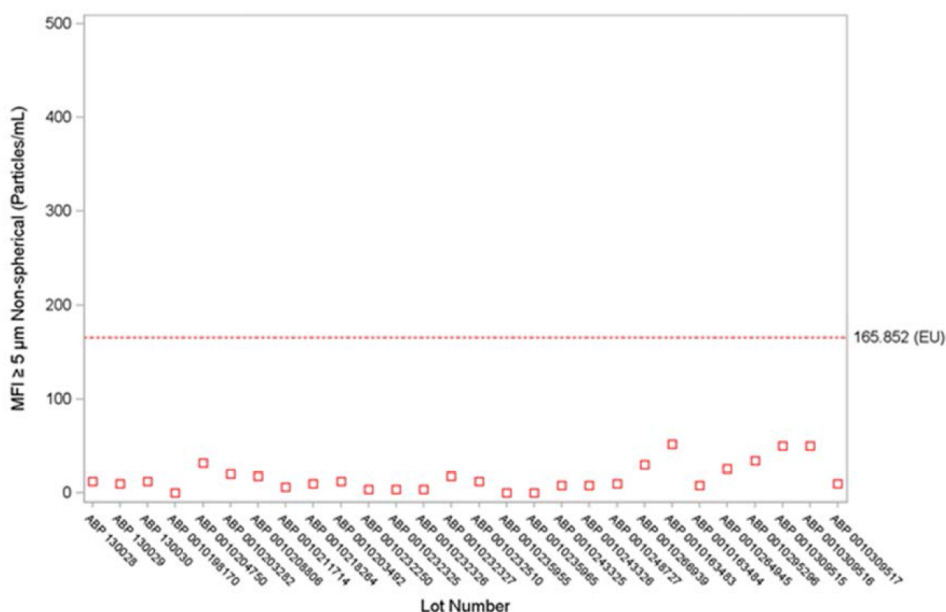
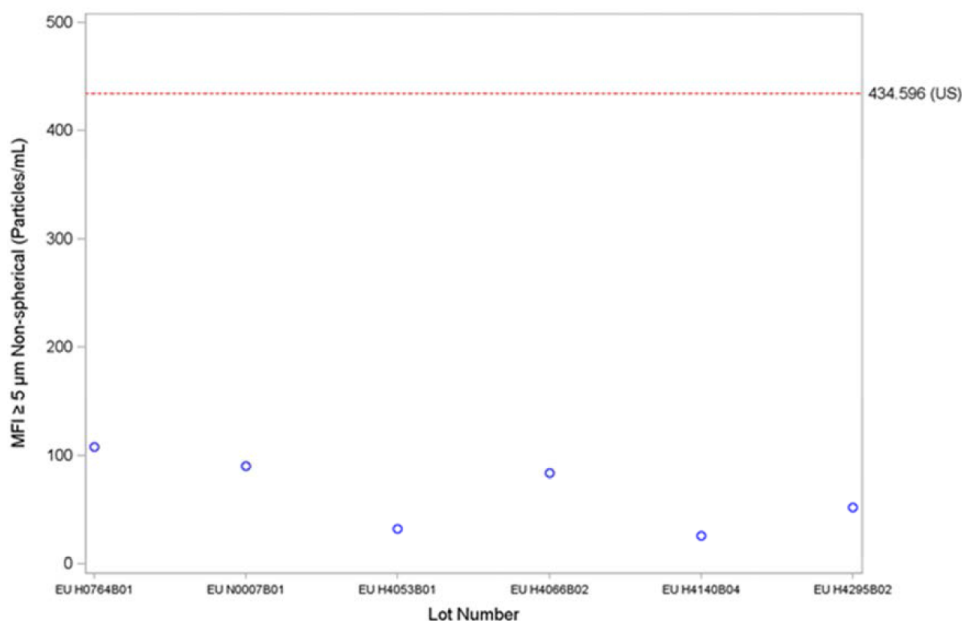


Figure 9. MFI $\geq 5 \mu\text{m}$ Non-spherical Subvisible Particles – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: The sponsor only used the upper limits of the quality ranges of US-licensed Herceptin and EU-approved Herceptin as the criteria in the similarity assessment. Since lower level of particles in ABP 980 lots than US-licensed Herceptin and EU-approved Herceptin is considered acceptable. Therefore, this is adequate.

The following conclusions were drawn.

- The $\geq 5 \mu\text{m}$ particles and $\geq 5 \mu\text{m}$ non-spherical subvisible particle results for ABP 980 are slightly lower than those found in US-licensed Herceptin and EU-approved Herceptin. The overall levels of $\geq 5 \mu\text{m}$ particles are very low. The slight differences observed would not preclude a determination of similarity for this attribute of the three products.
- All ABP 980 lots tested for the $\geq 5 \mu\text{m}$ non-spherical particles are within the quality ranges of both the US-licensed Herceptin and EU-approved Herceptin.
- EU-approved Herceptin tested for the $\geq 5 \mu\text{m}$ non-spherical particles are within the quality range of US-licensed Herceptin
- The data support a determination of high similarity between ABP 980 and US-licensed Herceptin. Additionally, the data provided support the adequacy of the scientific bridge to support the use of EU-approved Herceptin in clinical studies.

3.2.R.1.4.2 Submicron Particle (7:6:6)

Field Flow Fractionation (FFF) and Dynamic Light Scattering (DLS) were performed on 7 lots of ABP 980, 6 lots each of US-licensed Herceptin and EU-approved Herceptin.

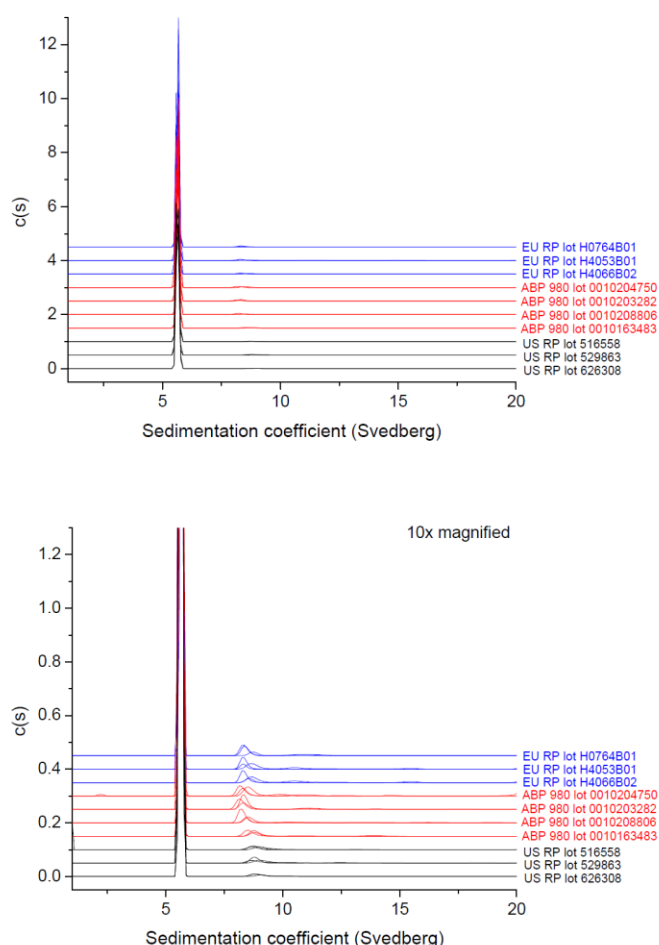
Submicron particles characterized by both FFF and DLS were evaluated as a Tier 3 attribute, and those FFF and DLS profiles are qualitatively compared. Testing results from the FFF and DLS are provided (not reproduced here).

Reviewer Comment: The FFF and DLS results indicate similar submicron particle profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.4.3 Analytical Ultracentrifugation Sedimentation Velocity (AUC-SV) (11:9:9)

The AUC-SV method measures the size distribution of the product in solution, including the presence of any higher molecular weight species (HMW). AUC-SV was performed on 11 lots of ABP 980, 9 lots each of US-licensed Herceptin and EU-approved Herceptin. AUC-SV profile was evaluated using a Tier 3 statistical method, while the HMW species level was considered a Tier 2 attribute. The results for all lots tested show that the levels of HMW species are below the LOQ of the method (3.7%), and the SV-AUC profiles are visually similar among the three products. Figure 14 below shows a representative comparison of SV-AUC profiles for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

Figure 14. SV-AUC Profiles for Trastuzumab (EU), ABP 980 (Clinical), and Trastuzumab (US)



Reviewer Comment: The AUC-SV method is considered orthogonal to SE-UHPLC. Consistent with the SE-UHPLC results, the AUC-SV results demonstrate similar SV-AUC profiles and levels of HMW

species between ABP 980 and US-licensed Herceptin; ABP 980 and EU-approved Herceptin; US-licensed Herceptin and EU-approved Herceptin.

3.2.R.1.4.4 Size Exclusion High Performance Liquid Chromatography with Light Scattering Detection (SE-HPLC-LS) (7:6:6)

The SE-HPLC-SLS method was used to characterize the molar masses of size variants. Seven ABP 980 lots were compared side-by-side against 6 lots each of US-licensed Herceptin and EU-approved Herceptin. Molar mass of main peak and pre-peak were assessed using a Tier 2 statistical method. The criteria for the determined molar masses of main peak and pre-peaks were set as 5% and 10% of the expected molar masses of product monomer (148 kDa) and dimer (296 kDa) based on assay variability. Light scattering profile comparison was evaluated as a Tier 3 attribute. Representative chromatograms comparing ABP 980 with US-licensed Herceptin and EU-approved Herceptin are presented in Figure 17 and Figure 19. The molar masses of the main peak and HMW species for each sample are provided in Table 8 and Table 9. The proposed criteria for molar masses of main peak and pre-peaks were met.

Figure 17. SE-HPLC-SLS - ABP 980 Clinical Lots and Trastuzumab (US)

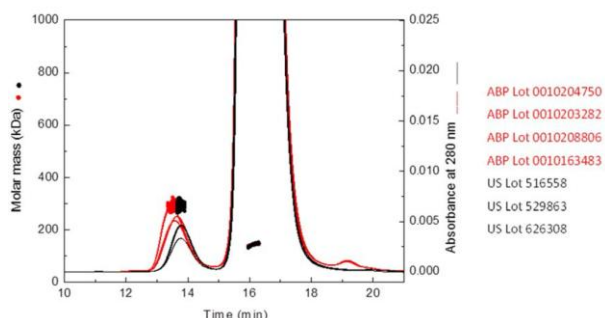


Figure 19. SE-HPLC-SLS - ABP 980 Clinical Lots and Trastuzumab (EU)

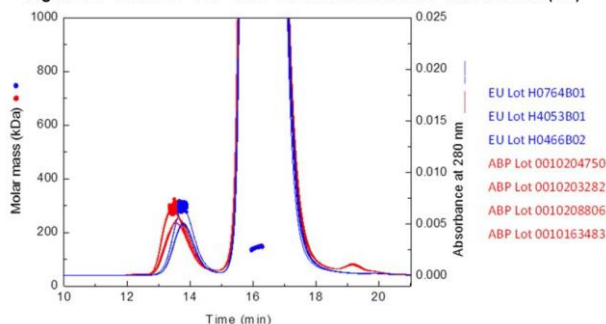


Table 8. SE-HPLC-SLS Results for Trastuzumab (EU), ABP 980 Clinical, and Trastuzumab (US)

	Main Peak (kDa)	Pre-peak (kDa)
EU H0764B01	143	303
EU H4053B01	144	302
EU H4066B02	144	289
ABP 0010204750	144	289
ABP 0010203282	144	281
ABP 0010208806	144	292
ABP 0010163483	144	307
US 516558	144	283
US 529863	144	289
US 626308	144	303

kDa = kilo Daltons

Table 9. SE-HPLC-SLS Results for Trastuzumab (EU), ABP 980 Validation, and Trastuzumab (US)

	Main Peak (kDa)	Pre-peak (kDa)
EU H4521H03	148	281
EU 4586H01	148	314
EU H4594H07	148	307
ABP 0010309515	148	293
ABP 0010309516	148	304
ABP 0010309517	148	318
US 3014299	148	290
US 3055922	148	312
US 3072720	148	313

kDa = kilo Daltons

Reviewer Comment: The data demonstrate that ABP 980 has similar SE-HPLC-LS profiles and molar masses for monomer and HMW species compared to those of the US-licensed Herceptin and EU-approved Herceptin. Data also support the conclusion that the majority of HMW species observed are dimeric. Additionally, data provided support the adequacy of the scientific bridge to support the use of EU-approved Herceptin in clinical studies.

3.2.R.1.5 Thermal Stability and Forced Degradation (4:3:3)

A thermal stability and degradation study was performed to evaluate the similarity of ABP 980 to US-licensed Herceptin and EU-approved Herceptin under the thermal forced degradation condition of 50°C for 28 days. The forced degradation study was conducted in a side-by-side manner. ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots used and their age at the initiation of the study are provided in Table 1. Samples for ABP 980 US-licensed Herceptin and EU-approved Herceptin were analyzed at intervals of 0, 1, 2, 3, and 4 weeks by SE-HPLC, rCE-SDS, nrCE-SDS, CEX-HPLC, and potency bioassay (proliferation inhibition assay).

Table 1. Drug Product Lots Used in the 50°C Forced Degradation Study

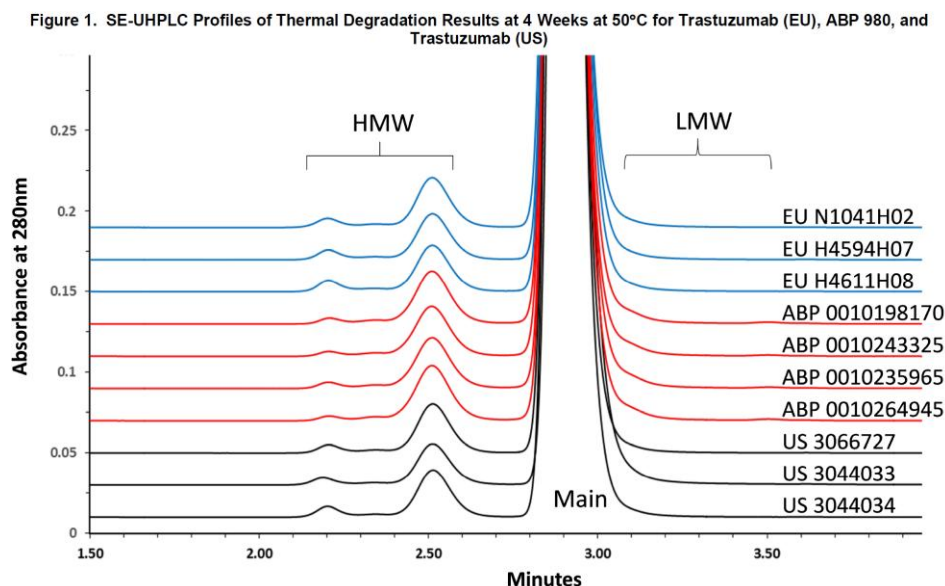
Lot	Estimated Material Age at Study Initiation (Months)
EU N1041H02	14
EU H4594H07	11
EU H4611H08	10
ABP 0010198170	26
ABP 0010243325	10
ABP 0010235965	11
ABP 0010264945	4
US 3066727	12
US 3044033	9
US 3044034	9

The sponsor states that accelerated (25°C) and stressed (40°C) stability studies were performed and the results (data not included in the submission) are consistent and support the overall conclusion of this 50°C forced degradation study.

Reviewer Comment: The results from accelerated (25°C) and stressed (40°C) stability studies were provided in the November 3, 2017 response to an IR. Unlike the forced degradation study at 50°C, these studies were not conducted in a side-by-side manner. However, data from these studies were reviewed and found consistent with the forced degradation study shown below. The results from accelerated (25°C) and stressed (40°C) stability studies support similar degradation pathways and rates for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

SE-UHPLC

The SE-UHPLC profiles of 4 ABP 980 lots, 3 US-licensed Herceptin lots, and 3 EU-approved Herceptin lots after incubation at 50°C for 28 days are overlaid in the figure below.



Reviewer Comment: The SE-UHPLC profiles are visually similar for all 3 products. Additionally, no new peaks are observed in ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin.

The degradation rate plots comparing % HMW species and main peak are provided in the figures below.

Figure 2. SE-UHPLC HMW for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

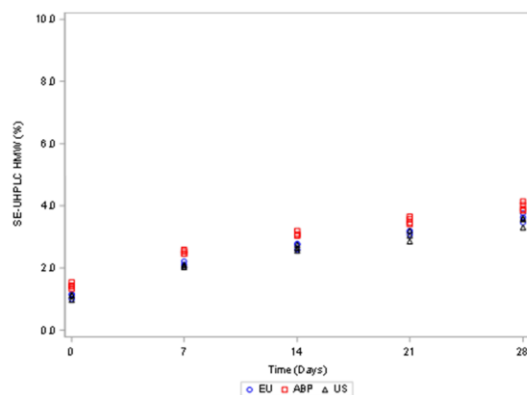
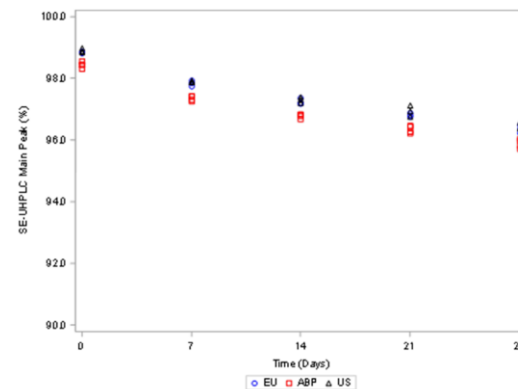


Figure 3. SE-UHPLC Main Peak for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

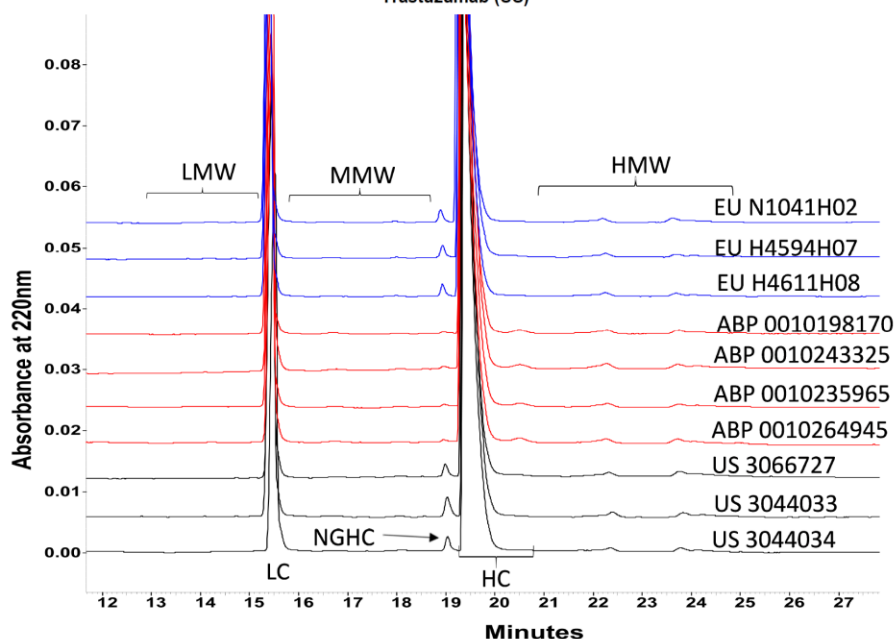


Reviewer Comment: Data support similar rCE-SDS forced degradation profiles and degradation rates among ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

rCE-SDS

The rCE-SDS profiles of 4 ABP 980 lots, 3 US-licensed Herceptin lots, and 3 EU-approved Herceptin lots after incubation at 50°C for 28 days are overlaid in the figure below.

Figure 4. rCE-SDS Profiles of Thermal Degradation Results at 4 Weeks at 50°C for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The degradation profiles are visually similar for all 3 products over 4 weeks at 50°C. No new peaks are observed in ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin. Consistent with rCE-SDS data discussed in section 3.2.R.1.3.2, a higher level of post-HC peak and a lower level of % NGHC were observed in ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin.

The degradation rate plots comparing % HC + LC, % LMW + MMW, and % NGHC are provided in Figures below.

Figure 5. rCE-SDS HC + LC for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

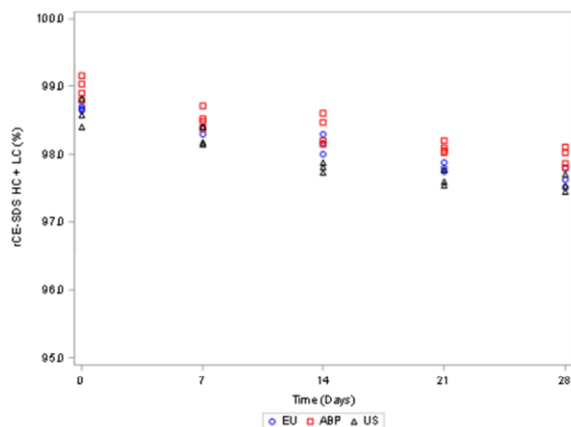


Figure 6. rCE-SDS LMW + MMW for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

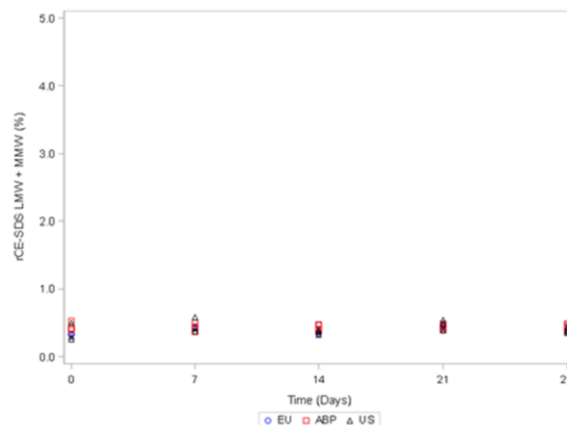
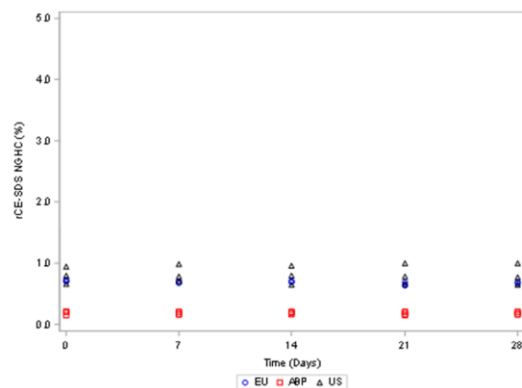


Figure 7. rCE-SDS NGHC for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

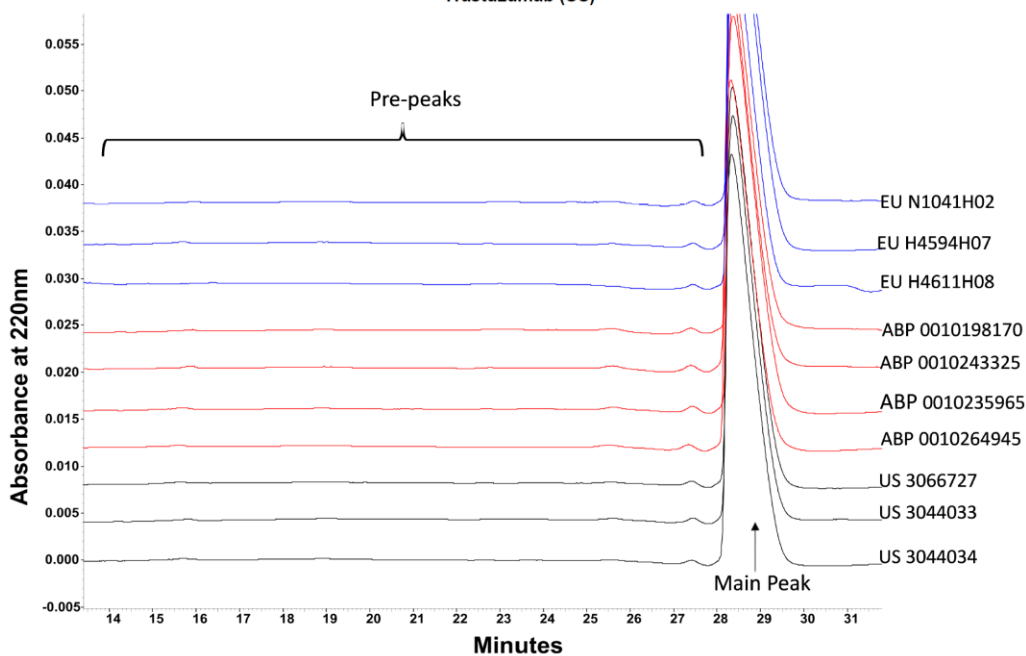


Reviewer Comment: The three products showed similar degradation rates with respect to % HC + LC. The differences in the level of HC + LC is due to the slightly lower level of NGHC consistently observed in ABP 980 lots compared to US-licensed Herceptin and EU-approved Herceptin lots, which is reviewed in section 3.2.R.1.3.2.

nrCE-SDS

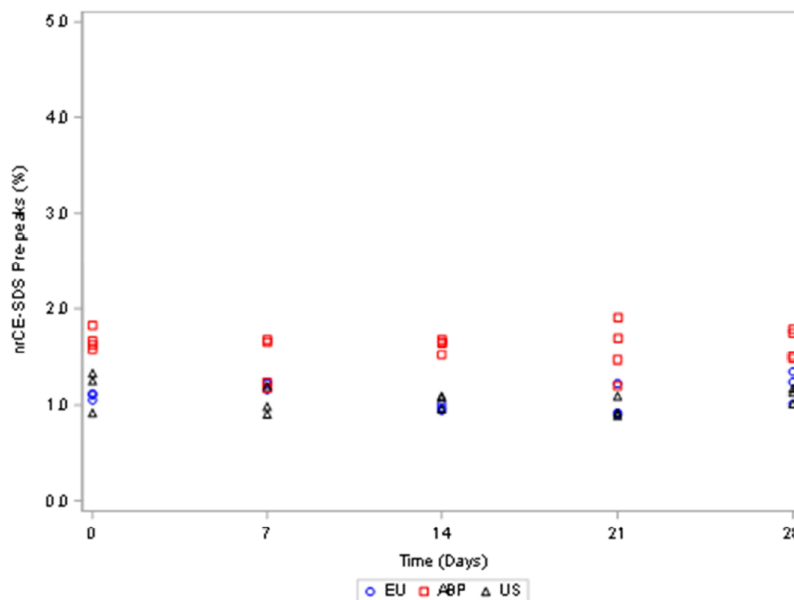
The rCE-SDS profiles of 4 ABP 980 lots, 3 US-licensed Herceptin lots, and 3 EU-approved Herceptin lots after incubation at 50°C for 28 days are overlaid in the figure below.

Figure 8. nrCE-SDS Profiles of Thermal Degradation Results at 4 Weeks at 50°C for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The degradation profile assessed by nrCE-SDS results are visually similar for all 3 products. No new peaks are observed in ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin.

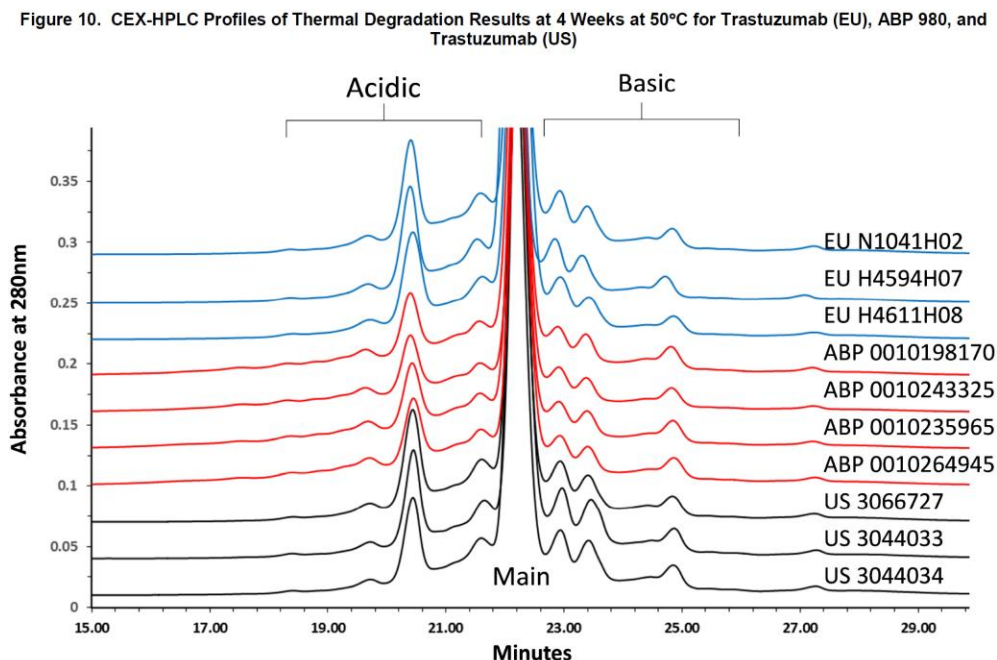
Figure 9. nrCE-SDS Pre-peaks for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C



Reviewer Comment: ABP 980 showed similar forced degradation rate by nrCE-SDS compared to US-licensed Herceptin and EU-approved Herceptin. EU-approved Herceptin and US-licensed Herceptin are similar with respect to forced degradation profile and rate.

CEX-HPLC

The CEX-HPLC profiles of 4 ABP 980 lots, 3 US-licensed Herceptin lots, and 3 EU-approved Herceptin lots incubated at 50°C for 4 weeks are overlaid in Figure 10 below.



Reviewer Comment: The three products show similar CEX-HPLC forced degradation profile with respect to acidic peaks, basic peaks, and main peak. The differences in the levels of acidic peaks, main peak, and basic observed between the three products are reviewed in section 3.2.R.1.3.2 Product-related Substances and Impurities.

The degradation rate plots comparing acidic peaks (Figure 11), main peak (Figure 12), and basic peaks (Figure 13) are provided in the following Figures 11-13, respectively.

Figure 11. CEX-HPLC Acidic Peaks for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

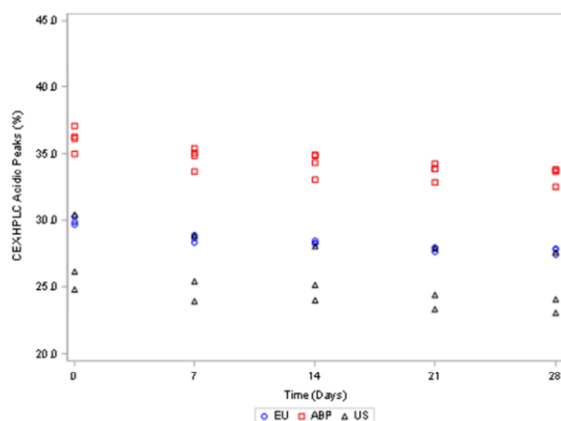


Figure 12. CEX-HPLC Main Peak for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

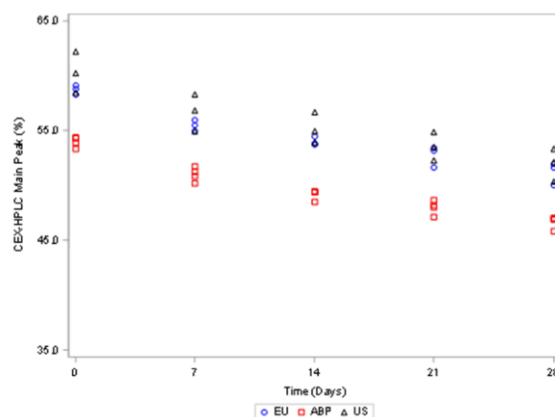
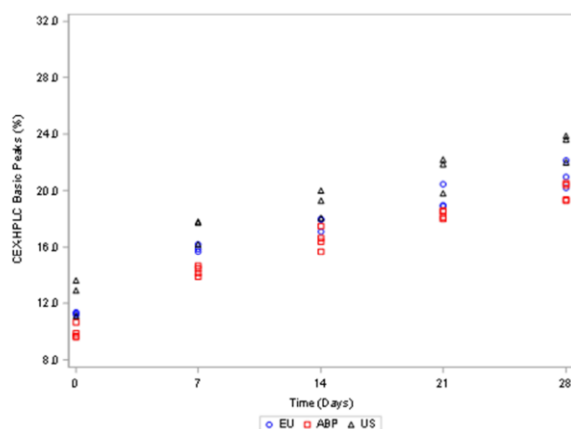


Figure 13. CEX-HPLC Basic Peaks for Trastuzumab (EU), ABP 980, and Trastuzumab (US) at 50°C

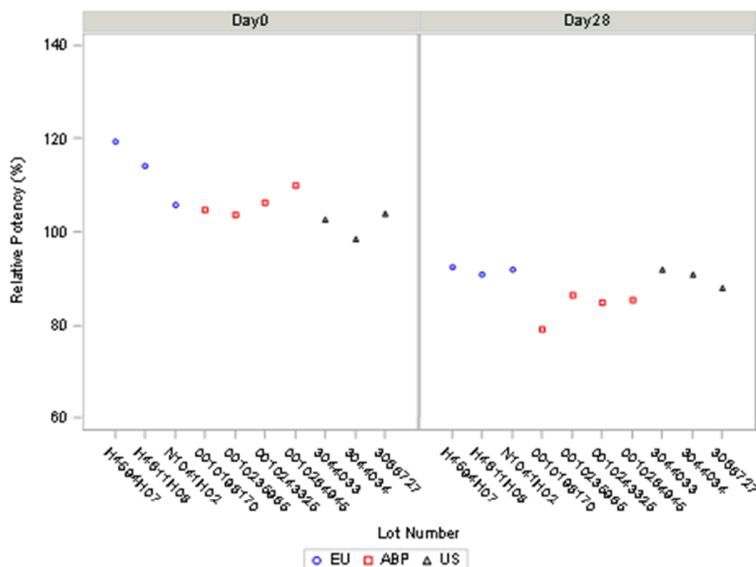


Reviewer Comment: The degradation rates of acidic peaks, main peak, and basic peaks are similar for the three products.

Proliferation Inhibition Bioassay (Potency)

The potency results between ABP 980, US-licensed Herceptin and EU-approved Herceptin are presented in Figure 14. Similar loss in potency after incubation at 50°C for 4 weeks was observed for all 3 products.

Figure 14. Relative Potency for Trastuzumab (EU), ABP 980, and Trastuzumab (US) on Day 0 and Day 28 at 50°C



Reviewer Comment for the Conclusion of the 50 °C Forced Degradation Study:

In conclusion, the degradation profiles for SE-HPLC, rCE-SDS, nrCE-SDS, CEX-HPLC, and potency assay are similar for ABP 980, US-licensed Herceptin and EU-approved Herceptin, and support a determination that ABP 980 is highly similar to US-licensed Herceptin. Additionally, the data support the analytical component of the scientific bridge to support the use of EU-approved Herceptin in clinical study.

3.2.R.1.6 General Properties

The similarity assessment of general properties for ABP 980, US-licensed Herceptin, and EU-approved Herceptin was evaluated by measuring lyophilized product protein concentration and protein content. Additional comparative characterization of reconstitution time is also included. The reconstituted protein concentration was classified as a Tier 2 attribute and the total protein content was assessed by Tier 3 criteria. For assessment of protein content, ABP 980 420 mg presentation (referred to in the submission as 440 mg) was compared to the US-licensed Herceptin 420 mg presentation, whereas ABP 980 150 mg presentation was compared to the EU-approved Herceptin presentation.

3.2.R.1.6.1 Protein Concentration and Protein Content (29:21:30)

Reviewer Comment: *The analytical procedure used for protein concentration is validated in section 3.2.S.4.3. The method used for protein content is detailed in 3.2.P.5.3.*

A total of 29 ABP 980 lots, 30 EU-approved Herceptin lots, and 21 US-licensed Herceptin lots were tested. The 150 mg presentations vials were reconstituted with 7.2 mL of WFI and 20 mL of WFI was needed for reconstitution of the 420 mg presentations. A comparison of protein content between ABP 980 and US-licensed Herceptin, ABP 980 and EU-approved Herceptin, is presented below. The results

show overlapping ranges between ABP 980 420 mg presentation and US-licensed Herceptin, and ABP 980 150 mg presentation and EU-approved Herceptin.

Figure 2. Protein Content Results for ABP 980 and Trastuzumab (US) for 440 mg Presentation

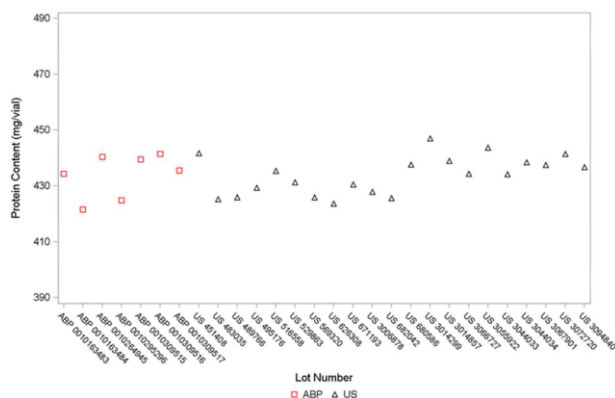
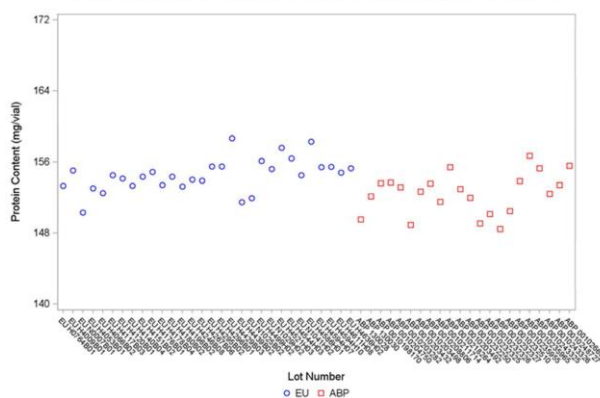


Figure 3. Protein Content Results for Trastuzumab (EU) and ABP 980 for 150 mg Presentation



Comparison of the reconstituted protein concentration among the three products is presented below. Twenty five out of 29 (86%) of the ABP 980 lots are within the US-licensed Herceptin quality range ($\text{Mean} \pm 3\text{xSD}$), while twenty six lots (90%) are within the EU-approved Herceptin quality range ($\text{Mean} \pm 3\text{xSD}$). Although a few ABP 980 lots are outside the quality ranges (four lots for US-licensed Herceptin, three lots for EU-approved Herceptin), the protein concentration of these lots is within 0.3 mg/mL of the ranges. Additionally, the lowest reconstituted protein concentration observed in ABP 980 (20 mg/mL) is within 5% of the target protein concentration (21 mg/mL). Therefore, the small difference is within the variability of reconstitution. The protein concentration of all EU-approved Herceptin lots are within the quality range of US-licensed Herceptin.

Figure 4. Reconstituted Protein Concentration – ABP 980 Compared to Trastuzumab (US) Quality Range

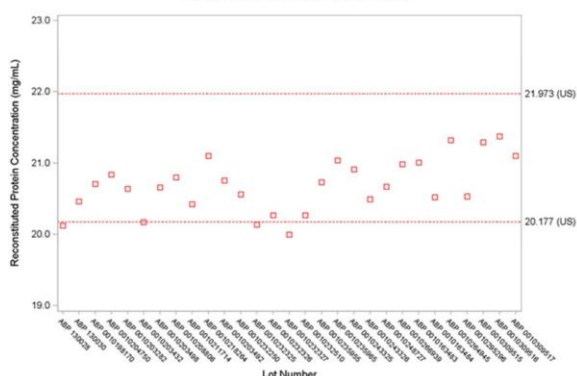


Figure 5. Reconstituted Protein Concentration – ABP 980 Compared to Trastuzumab (EU) Quality Range

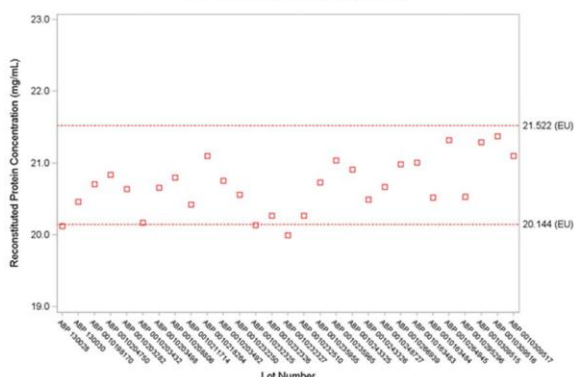
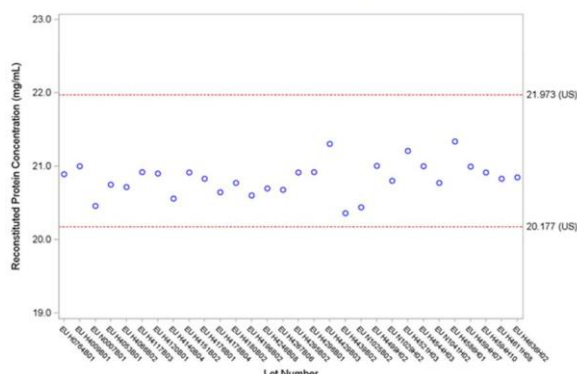


Figure 6. Reconstituted Protein Concentration – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: Amgen notes that commercial manufacturing controls for protein concentration were further optimized and data from process validation batches support better control of this attribute. Data support a determination of high similarity between ABP 980 and US-licensed Herceptin, and the adequacy of the scientific bridge to support the use of EU-approved Herceptin in clinical study.

3.2.R.1.6.2 Reconstitution time (30:3:3)

Thirty ABP 980 lots were compared with 3 lots each of US-licensed Herceptin and EU-approved Herceptin for reconstitution time. Reconstitution time was measured as the time (in seconds) from WFI injection into the vial to full dissolution of the lyophilized cake. The reconstitution time results for ABP 980, US-licensed Herceptin, and EU-approved Herceptin, are provided (not reproduced here). The results demonstrate that ABP 980 has a similar reconstitution time compared to US-licensed Herceptin and EU-approved Herceptin; and EU-approved Herceptin has a similar reconstitution time compared to US-licensed Herceptin.

Reviewer Comment: The maximum reconstitution time for ABP 980 is 93 seconds, which is well within the 300 second reconstitution time provided on the label for US-licensed Herceptin. Additionally, the differences in mean reconstitution time are within the standard deviation. For these reasons, data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Herceptin in clinical study 20120263.

3.2.R.1.7 Process-Related Impurities

Process-related impurities such as host cell protein (HCP), host cell DNA, and leached protein A, were characterized in ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The analysis of process-related impurities was intended to characterize any significant differences in ABP 980 that may pose risks on safety.

Reviewer Comment: *Process-related impurities are not expected to be identical among ABP 980, US-licensed Herceptin, and EU-approved Herceptin, given the difference in the cell line used and manufacturing process, but should be largely similar.*

3.2.R.1.7.1 Host Cell protein (HCP)

The residual HCP in ABP 980, US-licensed Herceptin, and EU-approved Herceptin were characterized and compared using the following methods:

- An HCP ELISA method that provides quantitative measurement of total HCP detected through the use of anti-HCP antibodies
- A 2-dimensional reverse phase liquid chromatograph (2D-LC) coupled with mass spectrometry (2D-LC-MSE) method

HCP measured by HCP ELISA and 2D-LC-MSE is considered a Tier 3 attribute. Additionally, a 2D-DIGE method was performed on ABP 980 and US-licensed Herceptin for characterization.

Host Cell Protein – ELISA (22:3:3)

The HCP ELISA method was performed on 22 ABP 980 drug substance lots and 3 lots each of US-licensed Herceptin and EU-approved Herceptin and results are listed in Table 1. A slightly higher HCP level (≤ 11 ng/mg) was measured compared to that in US-licensed Herceptin and EU-approved Herceptin. However, the overall levels of HCP are low in all 3 products, which would not have an adverse impact on safety.

Table 1. HCP ELISA Levels for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot	HCP (ng/mg) ^a	Lot	HCP (ng/mg) ^a	Lot	HCP (ng/mg) ^a
EU H4053B01	< 1	ABP 0010200648 ^b	6	US 516558	< 1
EU H4066B02	< 1	ABP 0010209656	7	US 529863	< 1
EU H4117B03	< 1	ABP 0010220792	7	US 626308	< 1
		ABP 0010229668	11		
		ABP 0010232685	6		
		ABP 0010239533	7		
		ABP 0010247558	7		
		ABP 0010253477	7		
		ABP 0010253479	11		
		ABP 0010253480	12		
		ABP 0010253481	10		
		ABP 0010253482	8		
		ABP 0010253484	7		
		ABP 0010262996	8		
		ABP 0010262997	8		
		ABP 0010262998	9		
		ABP 0010262999	6		
		ABP 0010292708	7		
		ABP 0010293548	8		
		ABP 0010294000	8		
		ABP 0010297878	8		
		ABP 0010302656	9		

ABP lot numbers are drug substance.

HCP = host cell protein

^a LOQ is 28 ng/mL (1 ng/mg).

^b Data from corresponding drug product Lot 0010163483

The units of ng/mg are converted using the sample protein concentrations (21 mg/mL).

Reviewer Comment: In the November 3, 2017 response to an IR, Amgen provided data to support that the HCP ELISA recognizes approximately 87% of potential HCP impurities. The overall levels of HCP detected by this method are low in ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Given that the in-house antiserum and HCP method are optimized to detect HCP in ABP 980, the minor differences in HCP levels for ABP 980 do not preclude demonstration of high similarity or the establishment of the analytical bridge.

Analysis by LC/MS (1:1:1)

A 2D-LC-HDMSE method was employed as an orthogonal assay to the HCP ELISA to identify individual host cell proteins. One ABP 980 lot and 1 lot each of US-licensed Herceptin and EU-approved Herceptin were tested. One residual HCP, heat shock cognate 71 kDa protein, was identified in all 3 lots at a relative level of 8 to 10 ppm. An additional residual HCP, zinc finger BED domain-containing protein 4, was identified in EU-approved Herceptin at a very low level of approximately 1 ppm.

Reviewer Comment: The 2D-LC-HDMSE results are consistent with the overall low levels of HCP detected by the HCP ELISA method for the three products.

Analysis by 2D-DIGE

One ABP 980 lot and one US-licensed Herceptin lot were analyzed by 2D-DIGE method on the same gel. The grayscale images of ABP 980 and US-licensed Herceptin are provided in Figure 1 and Figure 2, respectively. All spots of the 2D-DIGE images, including both product and residual HCP spots, were digitally analyzed. ABP 980 and US-licensed Herceptin were determined to be 95.5% similar.

Figure 1. Grayscale of ABP 980 (Lot 0010163483)

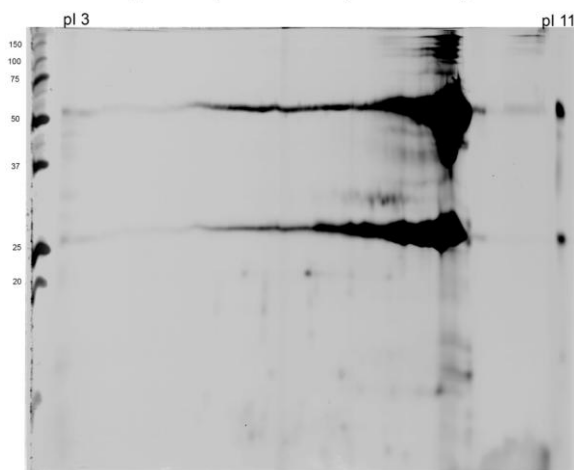
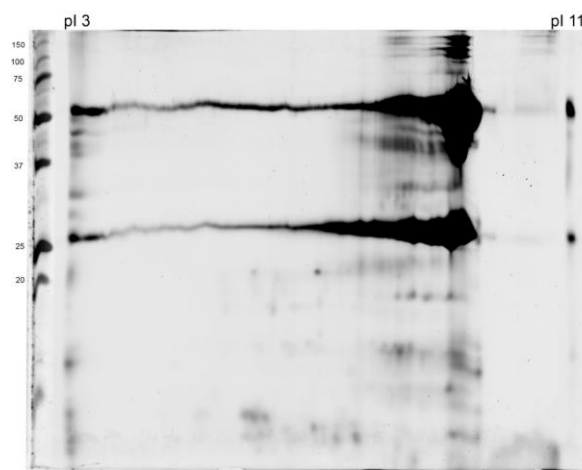


Figure 2. Grayscale of Trastuzumab (US) (Lot 529863)



3.2.R.1.7.2 Protein A – ELISA (22:3:3)

The protein A - ELISA method was performed on 22 ABP 980 drug substance lots and 3 lots of US-licensed Herceptin and EU-approved Herceptin. A summary of the assay validation characteristics are presented in the submission section 3.2.S.4.3 as this method was used throughout ABP 980 development. Levels of Protein A were below the assay limit of detection of 0.1 ng/mg for all three products.

Reviewer Comment: Protein A by ELISA is considered a Tier 3 attribute. Data support a determination of high similarity between ABP 980 and US-licensed Herceptin. Data also support the analytical bridge.

3.2.R.1.7.3 Residual DNA – Quantitative Polymerase Chain Reaction (22:3:3)

The residual DNA analysis by quantitative polymerase chain reaction (qPCR) was performed on 22 ABP 980 drug substance lots, and 3 lots each of US-licensed Herceptin and EU-approved Herceptin. A summary of the assay validation characteristics are presented in the submission section 3.2.S.4.4. Levels of DNA were below the assay limit of detection of 0.2 pg/mg for all three products.

Reviewer Comment: Data support that ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin with respect to this attribute, and EU-approved Herceptin is similar to US-licensed Herceptin with respect to this attribute.

3.2.R.1.8 Biological Activity

Reviewer Comment: Assays used for similarity assessment of the biological activities pertaining to the primary and secondary mechanisms of action for ABP 980, US-licensed Herceptin and EU-approved Herceptin, are summarized in the below table. Method qualification reports for the functional assays were provided in response to the IR dated October 25, 2017, and this information was considered during review of the similarity assessments.

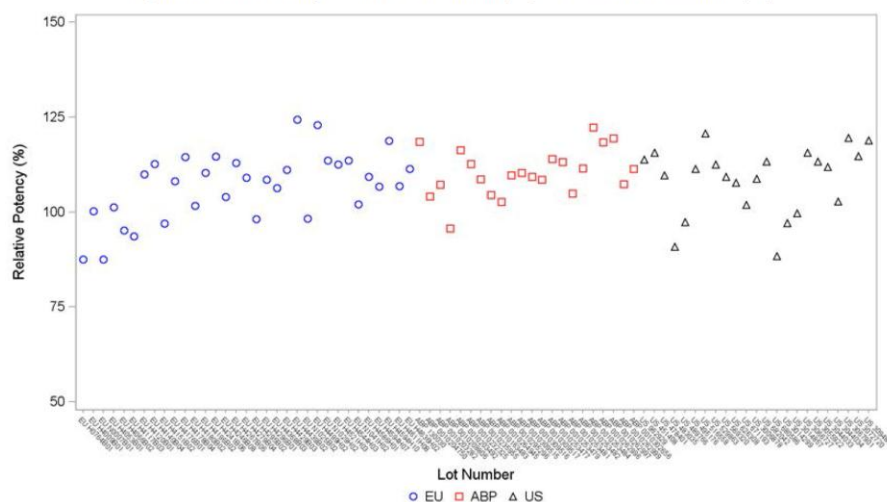
Analytical methods used for similarity assessment of the biological activities

Method	Relevant Activity	Tier
Proliferation inhibition bioassay (Potency)	HER2	1
Binding to HER2	HER2	1
ADCC	HER2 and FcR	1
Binding to FcγRIIIa(158V)	FcR	2
Binding to FcγRIIIa(158F)	FcR	2
Binding to FcRn	FcRn	2
Binding to C1q	C1q	3
CDC	HER2 and C1q	3
Additional Characterization		
HER2 Binding kinetics	HER2	3
Inhibition of AKT phosphorylation	HER2 and HER2-mediated signal	3
Inhibition of proliferation in NCI-N87 cells	HER2	3
Inhibition of Proliferation: Synergy with Chemotherapeutic in NCI-N87 cells	HER2	3
Lack of inhibition of proliferation in non-amplified HER2 cells		3
Lack of ADCC in non-amplified HER2 cells	HER2 and FcR	3
Binding to FcγRIa	FcR	3
Binding to FcγRIIa(131H)	FcR	3
Antibody-dependent cellular phagocytosis (ADCP)	FcR	3
Binding to FcγRIIb	FcR	3
FcγR binding on primary macrophages	FcR	3
Binding to FcγRIIb	FcR	3

3.2.R.1.8.1 Proliferation Inhibition Bioassay (Potency) (22:23:33)

The proliferation inhibition bioassay was performed using a breast cancer cell line (BT-474) with constitutively high levels of HER2 expression. This method is proposed as a specification test and is detailed in section 3.2.S.3.1 and section 3.2.S.4. Twenty-two ABP 980, 23 US-licensed Herceptin, and 33 EU-Approved Herceptin lots were tested for similarity assessment. Figure 1 shows the % relative potency of ABP 980, US-licensed Herceptin and EU-approved Herceptin relative to ABP 980 reference standard.

Figure 1. Relative Potency Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



The potency assay assesses the primary mechanism of action and is classified as a Tier 1 attribute. The results were evaluated using an equivalence test for similarity assessment.

Results of the equivalence test performed by Amgen on the lots of ABP 980 vs. US-licensed Herceptin, ABP 980 vs. EU-approved Herceptin, and US-licensed Herceptin vs. EU-approved Herceptin are presented below, demonstrating the potencies of the three products are statistically equivalent.

Table 2. Equivalence Test Results for Relative Potency – ABP 980 to Trastuzumab (US)

Assay/Attribute	ABP 980 Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative potency (%)	110.4796	108.4688	2.0109	-1.8450	5.8668	±13.3789	Equivalent

Table 3. Equivalence Test Results for Relative Potency – ABP 980 to Trastuzumab (EU)

Assay/Attribute	ABP 980 Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative potency (%)	110.4796	106.7863	3.6933	0.2722	7.1145	±13.3315	Equivalent

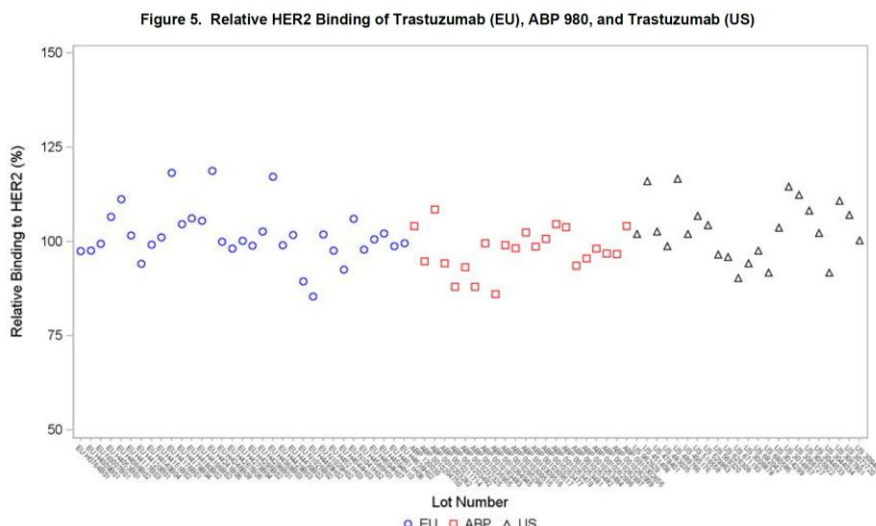
Table 4. Equivalence Test Results for Relative Potency – Trastuzumab (EU) to Trastuzumab (US)

Assay/Attribute	Trastuzumab (EU) Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative potency (%)	106.7863	108.4688	-1.6825	-5.7411	2.3761	±13.3789	Equivalent

Reviewer Comment: Review of the suitability of the statistical evaluation of equivalency for the potency was conducted by the CMC statistical review team in the Office of Biostatistics. These data support a determination of highly similar for ABP 980 to US-licensed Herceptin, and support the analytical bridge among the three products.

3.2.R.1.8.2 HER2 Binding by ELISA (22:23:33)

The HER2 binding was evaluated for ABP 980, US-licensed Herceptin, and EU-approved Herceptin using a solid phase enzyme-linked immunosorbent assay (ELISA). This method is described in section 3.2.S.3.1. Twenty-two ABP 980, 23 US-licensed Herceptin, and 33 EU-Approved Herceptin lots were tested for similarity assessment (Figure 5, below).



The HER2 binding assay assesses the primary mechanism of action and was evaluated by equivalence test (Tier 1). Results of the equivalence test performed by Amgen on the lots of ABP 980 vs. US-licensed Herceptin, ABP 980 vs. EU-approved Herceptin, and US-licensed Herceptin vs. EU-approved Herceptin are presented below. The results show that the confidence bounds on the difference in means between the three products fall within the EACs, demonstrating that the HER2 binding of the 3 products are statistically equivalent.

Table 6. Equivalence Test Results for HER2 Binding – ABP 980 to Trastuzumab (US)

Assay/Attribute	ABP 980 Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative binding to HER2 (%)	97.6788	102.9159	-5.2372	-8.6744	-1.7999	±11.6804	Equivalent

Table 7. Equivalence Test Results for HER2 Binding – ABP 980 to Trastuzumab (EU)

Assay/Attribute	ABP 980 Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative binding to HER2 (%)	97.6788	101.5495	-3.8707	-6.8237	-0.9177	±10.8088	Equivalent

Table 8. Equivalence Test Results for HER2 Binding – Trastuzumab (EU) to Trastuzumab (US)

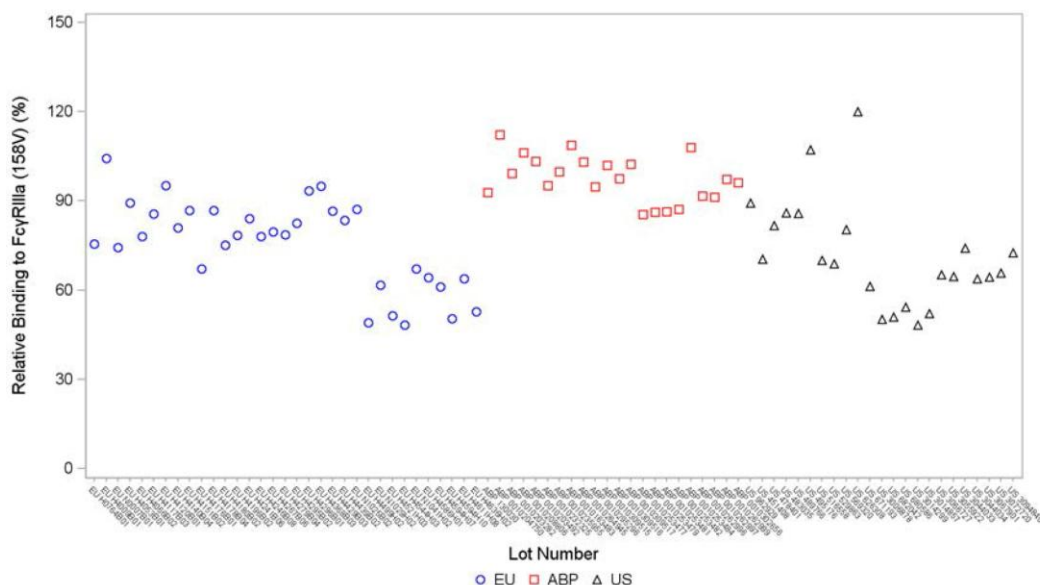
Assay/Attribute	Trastuzumab (EU) Mean	Trastuzumab (US) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative binding to HER2 (%)	101.5495	102.9159	-1.3664	-4.8122	2.0793	±11.6804	Equivalent

Reviewer Comment: Statistical equivalence tests are reviewed by CMC statistical reviewer. Although Amgen evaluated the HER2 binding using statistical equivalence criteria, the Agency currently considers Tier 2 quality range criteria are appropriate for this attribute. An IR was sent to Amgen requesting they perform Tier 2 evaluations of HER2 binding. Based on data provided in the submission, the 3xSD quality range for US-licensed reference product is (b) (4)%. This range would capture 100% of the ABP 980 lots and 100% of the EU-approved Herceptin lots. Therefore, these data support similar HER2 binding for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.8.3 FcγRIIIa (158V) Binding (22:23:33)

The FcγRIIIa (158V) binding assay assesses comparative binding of the Fc region to FcγR (158V), and is orthogonal to the antibody-dependent cellular cytotoxicity (ADCC) assay (see the section below) in assessing the biological property of Fc-mediated function. A competitive AlphaLISA binding assay was used and is detailed in 3.2.S.3.1 Elucidation of Structure and Other Characteristics. Twenty-two ABP 980 lots, 23 US-licensed Herceptin lots, and 33 EU-approved Herceptin lots were tested.

Figure 18. Relative Binding to FcγRIIIa (158V) Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: It is known that the levels of FcγRIIIa binding and ADCC activity of IgG1 antibodies are associated with the glycan distribution, such as afucosylated glycans and mannose. A relatively lower FcγRIIIa (158V) binding for US-licensed Herceptin and EU-approved Herceptin lots are observed over a period of time, which is consistent with the lower levels of afucosylated glycans and ADCC activity in these lots (refer to the section Glycan Distribution above and section ADCC activity below).

FcγRIIIa (158V) binding was evaluated using a Tier 2 statistical method against the quality ranges (Mean ± 3SD) of US-licensed H or EU-approved Herceptin lots. The figures below depict the FcγRIIIA (158V) binding results.

Figure 20. Relative Binding to FcγRIIIa (158V) – ABP 980 Compared to Trastuzumab (US) Quality Range

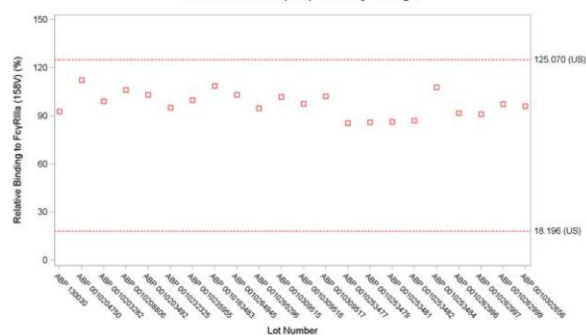


Figure 21. Relative Binding to FcγRIIIa (158V) – ABP 980 Compared to Trastuzumab (EU) Quality Range

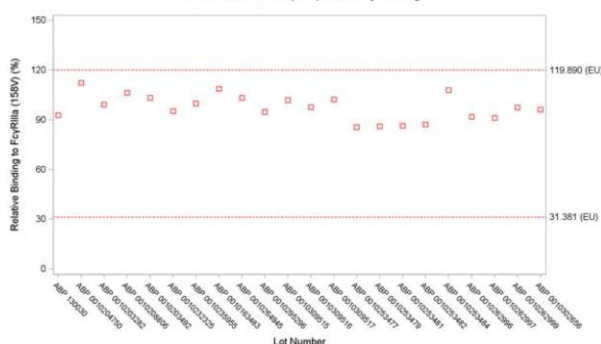
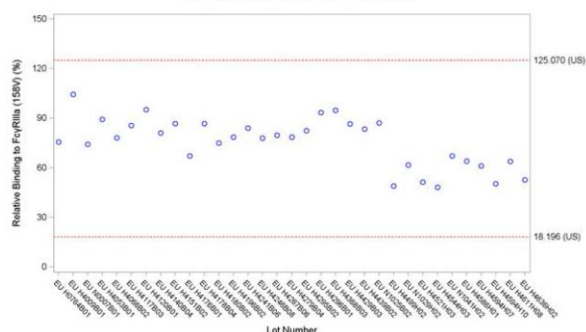


Figure 22. Relative Binding to FcγRIIIa (158V) – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range

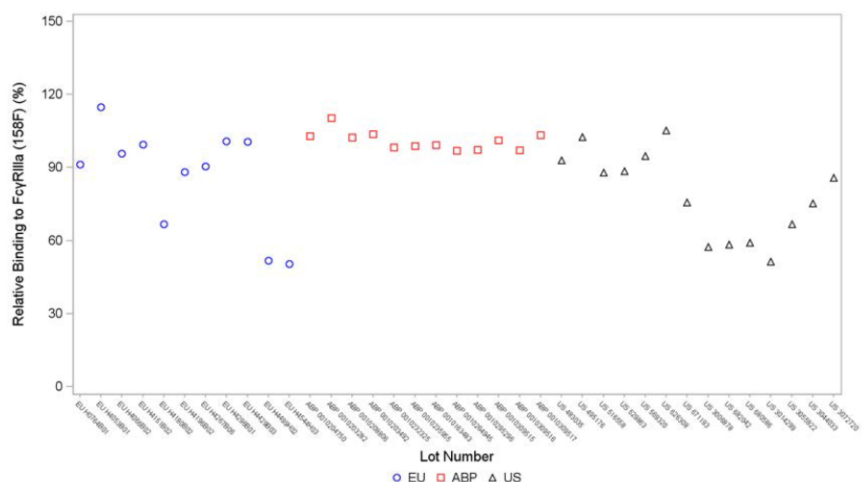


Reviewer Comment: Results demonstrated ABP 980 has similar FcγRIIIa (158V) binding compared to US-licensed Herceptin and EU-approved Herceptin, and EU-approved Herceptin has similar FcγRIIIa (158V) binding compared to US-licensed Herceptin. Data support a determination of high similarity for ABP 980 to US-licensed Herceptin, and support the three-way analytical bridge. Additionally, FcγRIIIa (158F) binding affinity was also evaluated using a Tier 2 statistical method, which supported the conclusion of similarity for this attribute for the three products (see the section below).

3.2.R.1.8.4 FcγRIIIa (158F) Binding (12:14:11)

The FcγRIIIa has 2 allelic variants. FcγRIIIa (158V) is the high affinity allotype, and occurs most frequently, whereas FcγRIIIa (158F) occurs less frequently and has a lower binding affinity to Fc. A competitive AlphaLISA™ binding assay was used to assess the binding of 12 lots of ABP 980, 14 lots of US-licensed Herceptin, and 11 lots of EU-Approved Herceptin to FcγRIIIa (158F). This assay is analogous to the FcγRIIIa (158V) binding assay, except that the acceptor beads are coated with recombinant human FcγRIIIa (158F).

Figure 25. Relative Binding to FcγRIIIa (158F) Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: Similar to FcγRIIIa (158V) binding results, a relatively lower FcγRIIIa (158F) binding was observed for US-licensed Herceptin and EU-approved Herceptin lots over a period of time.

The results for ABP 980 lots tested were assessed by the quality ranges (Mean $\pm$ 3xSD) established from 13 lots of US-licensed Herceptin or 11 lots of EU-approved Herceptin lots. The figures below depict the FcγRIIIa (158F) binding results.

Figure 26. Relative Binding to FcγRIIIa (158F) – ABP 980 Compared to Trastuzumab (US) Quality Range

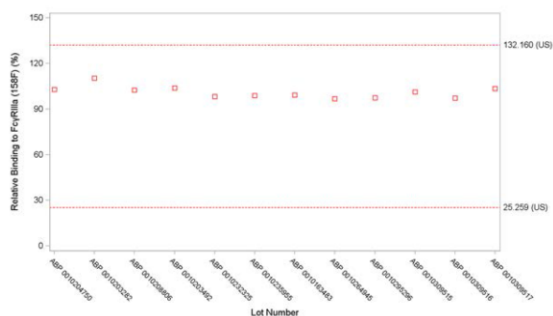


Figure 27. Relative Binding to FcγRIIIa (158F) – ABP 980 Compared to Trastuzumab (EU) Quality Range

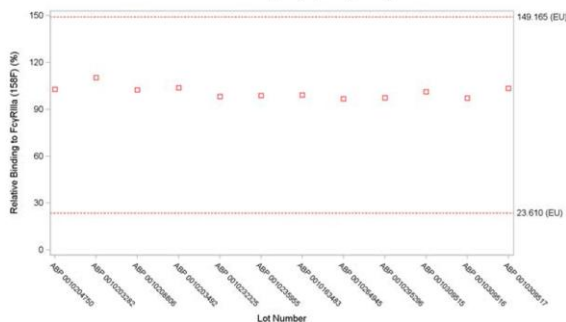
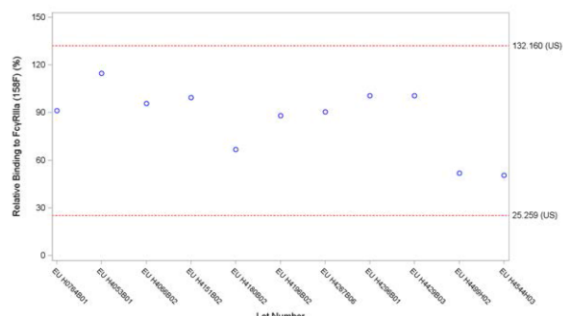


Figure 28. Relative Binding to FcγRIIIa (158F) – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: Data support that ABP 980 are similar to US-licensed Herceptin and EU-approved Herceptin with respect to their level of FcγRIIIa (158F) binding.

3.2.R.1.8.5 Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

ADCC activity is a potential mechanism of action for ABP 980 and is therefore evaluated by Tier 1 statistical equivalence criteria. Two ADCC assays, based on different effector cell populations (PBMC and NK cells), were employed to assess the biological activity of Fc-mediated effector function for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

PBMC-ADCC Activity

In the original BLA, Amgen provided ADCC data from an NK92 ADCC method only, which are reviewed in the next section below. In response to an IR sent on February 8, 2018, the company provided ADCC data from a second method that uses peripheral blood mononuclear cells (PBMC) isolated from donors heterozygous for FcγRIIIa (158V/F) alleles as effector cells, and SKBR3 HER2-expressing breast cancer cells as target cells (referred to as PBMC ADCC). The assay read-out is luminescence from a cytotoxicity reagent that measures quantity of intracellular protease released into the medium from compromised cells (i.e., dead-cell protease). PBMC ADCC results were provided from the same lots of ABP 980, US-licensed Herceptin, and EU-approved Herceptin as in the original BLA. Results from 5 lots of EU-approved Herceptin, for which no PBMC data were available at the time of the February 8, 2018 IR (lots EU H4120B01, EU H4241B06, EU H4279B04, EU H4368B03, and EU H4594H10), were later submitted by amendment to complete the dataset (refer to response to IR dated March 19, 2018). The Figure below provides the PBMC ADCC results, with US-licensed and EU-approved Herceptin lots arranged by expiry date along the x-axis from earliest (left) to most recent (right) expiry dates.

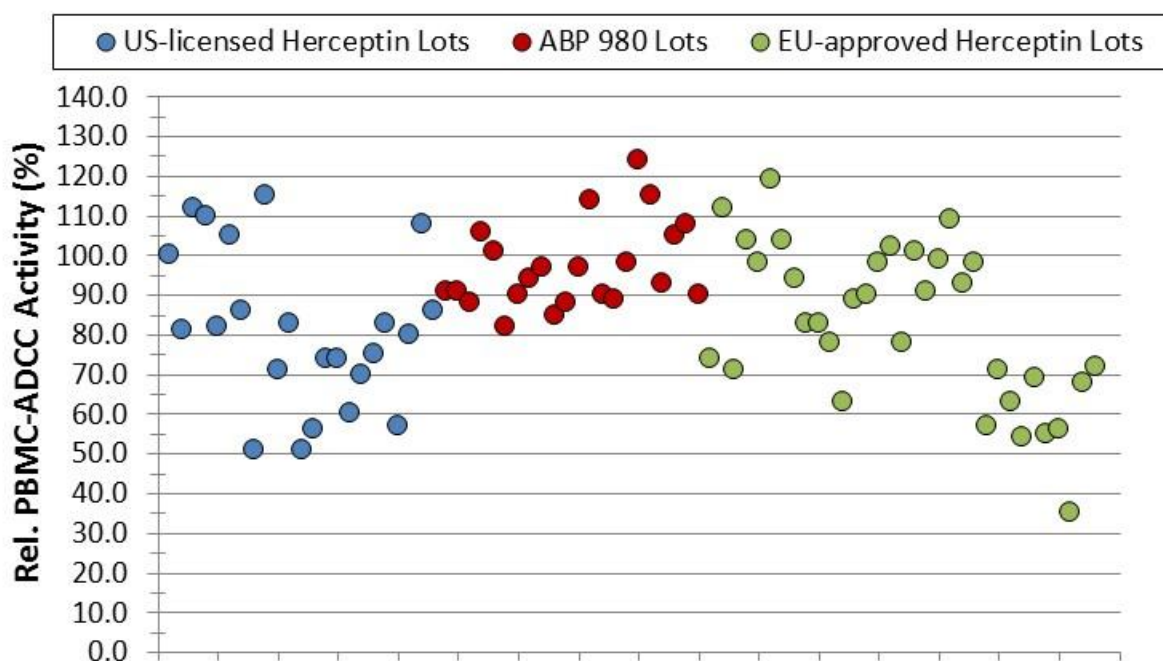


Figure generated by reviewer

Amgen applied Tier 1 statistical equivalence testing based on mean values to assess whether PBMC ADCC results for ABP 980 lots are statistically equivalent to US-licensed and EU-approved Herceptin lots, and whether US-licensed Herceptin lots are statistically equivalent to EU-approved Herceptin lots.

All three comparisons met statistical equivalence criteria. Tables 5, 9, and 10 shown below provide results from the statistical analyses of ADCC data generated from the PBMC method.

Table 5. Mean-Based Equivalence Test Results for Relative ADCC by PBMC – ABP 980 to Trastuzumab (US)

Assay/Attribute	Trastuzumab (US) Mean	ABP 980 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	81.16	97.06	15.90	7.92	23.88	±29.58	Equivalent

Table 9. Equivalence Test Results for Relative PBMC ADCC – ABP 980 to Trastuzumab (EU)

Assay/Attribute	Trastuzumab (EU) Mean	ABP 980 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	82.76	97.06	14.30	7.31	21.30	± 29.93	Equivalent

Table 10. Equivalence Test Results for Relative PBMC ADCC – Trastuzumab (EU) to Trastuzumab (US)

Assay/Attribute	Trastuzumab (US) Mean	Trastuzumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by PBMC (%)	81.16	82.76	1.60	-7.43	10.62	±29.58	Equivalent

Reviewer Comment:

These results support similar ADCC activity for ABP 980, US-licensed Herceptin, and EU-approved Herceptin when using PBMC as effector cells. CMC statisticians confirmed Amgen's results. PBMC include effector cells with Fc receptors that can mediate ADCC activity. Although PBMC ADCC data were not requested by FDA, the use of PBMC-based ADCC methods was previously reviewed by the Agency and found acceptable to support demonstration of statistically equivalent ADCC activity for proposed trastuzumab biosimilars (refer to meeting materials for the July 13, 2017 Oncologic Drugs Advisory Committee Meeting Materials, located on the FDA website). Therefore, based on this precedent and justification, the PBMC ADCC data were accepted during the review cycle for the Tier 1 statistical evaluation of ADCC activity of ABP 980 as part of demonstrating similarity.

NK92-ADCC Activity

Amgen originally assessed ADCC activity by an orthogonal method that uses engineered natural killer (NK) cells as effectors (referred to as NK92 ADCC assay). By this method, HCC2218 cells that stably express high levels of HER2 on cell surface are used as target cells while NK92-M1 cells, which are stably transfected with human FcγRIIIa (also known as CD16), are used as effector cells. For similarity assessment, 22 ABP 980 lots, 23 US-licensed Herceptin lots, and 33 EU-approved Herceptin lots were tested for NK92 ADCC activity and evaluated using statistical equivalence tests. Low values of ADCC activity were observed for certain US-licensed Herceptin and EU-approved Herceptin lots. Amgen states the following in the BLA: "Low values of ADCC activity were first observed for trastuzumab (US) and trastuzumab (EU) lots with expiry of August, 2018 (US 671193 and EU 4499H02) as shown in Figure 29. This downward shift in ADCC activity for trastuzumab (US) and trastuzumab (EU) is consistent

with that reported in literature (Kim, 2017).” Given the lower ADCC activity in certain US-licensed Herceptin and EU-approved Herceptin lots, Amgen performed a Tier 1 similarity assessment for ADCC activity using two equivalence tests based on the mean and standard deviation, as well as the median and interquartile range. The mean-based equivalence test also shows equivalence criteria are met for comparisons between ABP 980 and EU-approved Herceptin, as well as EU-approved Herceptin and US-licensed Herceptin; however, ABP 980 and US-licensed Herceptin did not meet equivalence criteria.

Reviewer Comments:

- *The Tier 1 statistical methodology and evaluation of equivalency for the ADCC results were reviewed by the Office of Biostatistics. The mean-based statistical results based on the NK92 cell ADCC assay supported equivalence of ADCC activity between US-licensed Herceptin and EU-approved Herceptin, and between ABP 980 and EU-approved Herceptin. However, mean-based statistics based on the NK92 cell ADCC assay did not support equivalence between ABP 980 and US-licensed Herceptin.*
- *Amgen claimed that “the mean-based equivalence test shows a not-equivalent result due to the downward shift in ADCC values observed in trastuzumab (US) lots,” which the company attributes to US-licensed Herceptin lots with expiry dates starting in August 2018. To evaluate this claim, FDA conducted mean-based statistical equivalence analyses on the NK92 ADCC data and found that US-licensed Herceptin lots with expiry dates earlier than August 2018 are also not equivalent to ABP 980. These results contradict Amgen’s contention that ABP 980 would have met mean-based statistical equivalence with US-licensed Herceptin were it not for what Amgen asserts was a “downward shift in ADCC values” of the reference product.*

In response to the February 8, 2018 IR, Amgen provided NK92 ADCC data from 6 additional lots of US-licensed Herceptin tested after submitting the original BLA. The additional lots of US-licensed Herceptin (US 3179410, US 3191001, US 3195645, US 3197057, US 3195644, and US 3185091) have expiry dates of March 2021, May 2021, or June 2021, which are more recent than lots provided in the original BLA. NK92 ADCC values for the 6 additional reference product lots range from 93-105%, which are all higher than the mean NK92 ADCC value of 71.9% for lots provided in the original BLA. The Figure below provides the amended NK92 ADCC results, with US-licensed and EU-approved Herceptin lots arranged by expiry date along the x-axis from earliest (left) to most recent (right) expiry dates; the red bracket was added by the reviewer to mark the 6 additional lots.

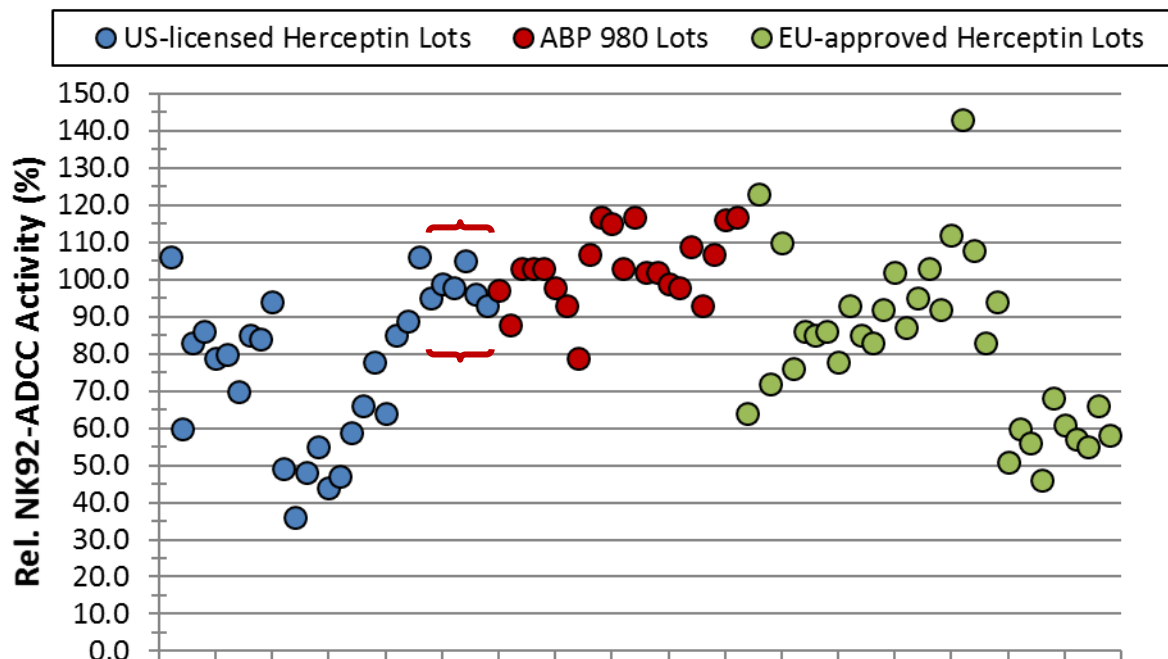


Figure generated by reviewer

Amgen applied Tier 1 statistical equivalence testing based on mean values to assess whether amended NK92 ADCC results for ABP 980 lots are statistically equivalent to US-licensed Herceptin lots. Statistical equivalence criteria for NK92 ADCC results were not met for ABP 980 lots compared with US-licensed Herceptin. Table 3 shown below provides results from the statistical analyses of amended ADCC data generated by the NK92 method.

Table 3. Mean-based Equivalence Test Results for Relative ADCC by NK92 – ABP 980 to Trastuzumab (US)

Assay/Attribute	Trastuzumab (US) Mean	ABP 980 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative ADCC by NK92 (%)	77.20	102.97	25.76	18.44	33.08	±30.79	Not Equivalent

Reviewer Comments on ADCC Activity based on NK92 cell assays and PBMC assay:

In evaluating these data, I considered the following:

- Results from the PBMC ADCC similarity assessment support similar ADCC activity. Amgen argues that the PBMC method is more physiologically relevant than the engineered NK92 assay. Although with the available evidence, it is not possible to conclude that the PBMC assay is superior to the NK92 cell-based assay with respect to in vivo activity, the PBMC assay does include populations of effector cells that can mediate ADCC in the context of trastuzumab treated breast cancer. Moreover, use of PBMC ADCC assays have been found acceptable to evaluate ADCC activity for other trastuzumab biosimilar programs. For these reasons, the use of the PBMC assay is adequate for the ABP 980 analysis.
- A period of out-of-trend (low) results in the innovator product lots (US-licensed Herceptin and EU-approved Herceptin) impacted the statistical equivalence testing on NK92 ADCC data.

Furthermore, these findings correlated with out-of-trend distributions of glycan and *FcγRIIIa* binding data observed for the same lots, and independently corroborated by published data. For example, the study referenced by Amgen (Kim, et.al. 2017. MABS. 9(4):704) demonstrated decreased levels of % afucose (G0+G1+G2) in US-licensed Herceptin and EU-approved Herceptin lots over a similar period of time concomitant with downward trends in *FcγRIIIa* binding and ADCC activity. Nevertheless, data from Amgen from more recent lots of US-licensed Herceptin show an upward trend in NK92 ADCC and correlated glycan patterns. This recent upward trend further suggests that the difference in ADCC activity between ABP 980 and marketed US-licensed Herceptin might be overestimated by the current NK92 ADCC dataset.

- Afucosylation percentage results and *FcγRIIIa* binding, which are correlated with ADCC, are similar between ABP 980 and US-licensed Herceptin. Demonstration of similarity for multiple quality attributes that are tightly linked to ADCC activity further support the conclusion that minor differences observed in NK92 ADCC activity do not preclude a demonstration of high similarity.

Collectively, the data indicates that ABP 980 has similar ADCC activity to US-licensed Herceptin, and the data support that ABP 980 is highly similar to US-licensed Herceptin.

3.2.R.1.8.6 FcRn Binding (22:22:33)

The FcRn binding assay assesses comparative binding of the Fc region to FcRn, which contributes to the PK of the molecule. A competitive AlphaScreen FcRn binding assay was developed to assess the binding of ABP 980, US-licensed Herceptin, and EU-approved Herceptin to FcRn. The method is detailed in 3.2.S.3.1 Elucidation of Structure and Other Characteristics. The FcRn binding method was performed on 22 lots each of ABP 980 and US-licensed Herceptin, and 33 EU-approved Herceptin lots. For similarity assessment, the FcRn binding was classified as Tier 2 attributes. Each ABP 980 lot was compared against the quality ranges (Mean $\pm$ 3xSD) of US-licensed Herceptin. ABP 980 lots were also compared against a separate quality range (Mean $\pm$ 3xSD) based on EU-approved Herceptin. Additionally, each EU-approved Herceptin was compared against the quality ranges of US-licensed Herceptin. The results are presented below. Twenty one of the 22 ABP 980 lots (95%) are within the quality ranges of US-licensed Herceptin and EU-approved Herceptin. All EU-approved Herceptin lots are within the quality ranges of US-licensed Herceptin.

Figure 15. Relative Binding to FcRn – ABP 980 Compared to Trastuzumab (US) Quality Range

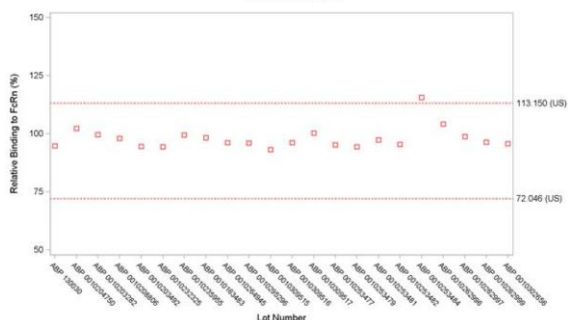


Figure 16. Relative Binding to FcRn – ABP 980 Compared to Trastuzumab (EU) Quality Range

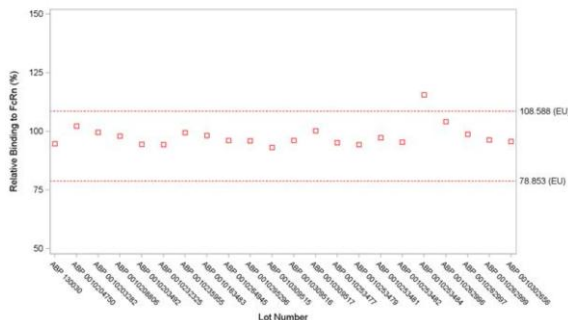
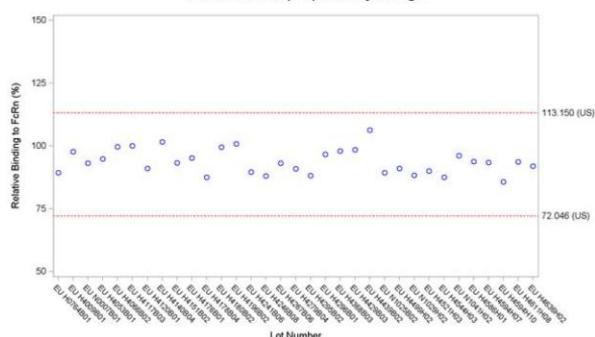


Figure 17. Relative Binding to FcRn – Trastuzumab (EU) Compared to Trastuzumab (US) Quality Range



Reviewer Comment: Results demonstrated that ABP 980 has similar FcRn binding compared to US-licensed Herceptin and EU-approved Herceptin; and EU-approved Herceptin is also similar to US-licensed Herceptin with respect to FcRn binding. These data support a determination of high similarity between ABP 980 and US-licensed Herceptin. Additionally, the data provided support the adequacy of the analytical bridge.

3.2.R.1.8.7 C1q Binding (11:10:10)

Binding to C1q was assessed using a direct binding ELISA, where bound C1q is detected using an anti-C1q horseradish peroxidase conjugated antibody. Eleven ABP 980 lots; and 10 lots each of US-licensed Herceptin and EU-approved Herceptin were tested. The Sponsor stated that “the C1q binding assay was performed on lots comprised of trastuzumab (US) and trastuzumab (EU) lots before and after the observed shift in ADCC activity.” Results for each lot are plotted as dose-response curves and fit to a 5-parameter logistic model. Binding to C1q is classified as a Tier 3 attribute for similarity assessment due to the absence of CDC function for the three products (refer to the CDC section below). The C1q binding data provided are summarized below, in a table directly copied from the submission.

Table 23. C1q Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	Relative C1q Binding (%)	Lot Number	Relative C1q Binding (%)	Lot Number	Relative C1q Binding (%)
EU H0764B01	79	ABP 130030	101	US 962929	100
EU H4009B01	101	ABP 0010204750	98	US 516558	96
EU H4053B01	94	ABP 0010203282	107	US 529863	87
EU H4066B02	90	ABP 0010208806	107	US 626308	108
EU H4246B08	88	ABP 0010203492	108	US 671193	98
EU H4521H03	72	ABP 0010232325	118	US 3014299	85
EU H4544H03	74	ABP 0010235955	112	US 3014857	89
EU N1041H02	92	ABP 0010163483	118	US 3055922	92
EU H4586H01	90	ABP 0010309515	109	US 3044033	83
EU H4594H07	102	ABP 0010309516	134	US 3072720	107
		ABP 0010309517	124		
EU mean	88	ABP mean	112	US mean	95
EU SD	10	ABP SD	10	US SD	9
EU min to max range	72 to 102	ABP min to max range	98 to 134	US min to max range	83 to 108

Reviewer Comment: Overall the C1q binding results show relatively higher binding for ABP 980 compared to US-licensed Herceptin and EU-approved Herceptin. Given that there is no CDC activity exhibited for all three products, this difference would not preclude determination of high similarity of ABP 980 to US-licensed Herceptin or the adequacy of the analytical bridge.

3.2.R.1.8.8 Complement-dependent Cytotoxicity (CDC) (1:1:1)

It is known that US-licensed Herceptin and EU-approved Herceptin lack CDC activity. The CDC assay was performed on 1 lot each of ABP 980, US-licensed Herceptin, and EU-approved Herceptin to assess if ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin regarding CDC activity. The CDC activity is assessed as a Tier 3 attribute.

For the CDC assay, HCC2218 cells, which overexpress HER2, are used as target cells. The HCC2218 cells are loaded with calcein-AM. This reagent readily enters cells where it is cleaved by nonspecific esterases to become fluorescent and trapped within the cell membrane. The calcein loaded target cells are first incubated with different dose concentrations of antibody, then complement is added. After the complement incubation, the supernatant is removed and the fluorescence is measured using a microplate reader. The fluorescence intensity is directly proportional to the amount of cellular lysis. The CDC assay results demonstrate a lack of CDC activity for all three products.

Reviewer Comment: The data support a determination of similarity regarding the lack of CDC activity among the three products

3.2.R.1.8.9 HER2 Binding Kinetics by SPR (4:3:3)

A surface plasmon resonance (SPR) method was utilized to characterize the HER2 binding kinetics of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. This method is orthogonal to the HER2 binding ELISA and is considered a Tier 3 assay. Briefly, samples were captured on the ProteOn® chip surface using a goat-anti-human IgG1 antibody and then bind to recombinant human HER2 ranging between 0.309 nM and 25 nM. Results are reported as the average of 3 intra-assay replicates per lot. A

long dissociation phase experiment was also performed at 25 nM recombinant human HER2. For similarity assessment, four ABP 980 lots, 3 lots each of US-licensed Herceptin and EU-Approved Herceptin lots were tested in one side-by-side experiment. The association and dissociation rate constants (k_a , k_d), and the dissociation equilibrium binding constant (K_d) are summarized in Table 9. The differences in HER2 kinetic binding (k_a , k_d , and K_d) observed among the three products are within the assay variability.

Table 9. Summary of Kinetic Rate and Binding Constants for Recombinant HER2 Binding to Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	k_a ($M^{-1}s^{-1}$) $\times 10^5$	k_d (s^{-1}) $\times 10^{-5}$	K_d (pM)
EU H0764B01	6.33	5.77	91.6
EU H4053B01	6.99	4.41	63.0
EU H4066B02	6.67	4.64	69.0
ABP 130028	6.64	4.98	75.3
ABP 0010204750	6.61	5.16	78.7
ABP 0010203282	6.54	4.91	74.9
ABP 0010163483	6.65	5.13	76.7
US 516558	6.67	5.34	79.5
US 529863	7.30	4.90	67.1
US 569320	7.24	5.37	74.6

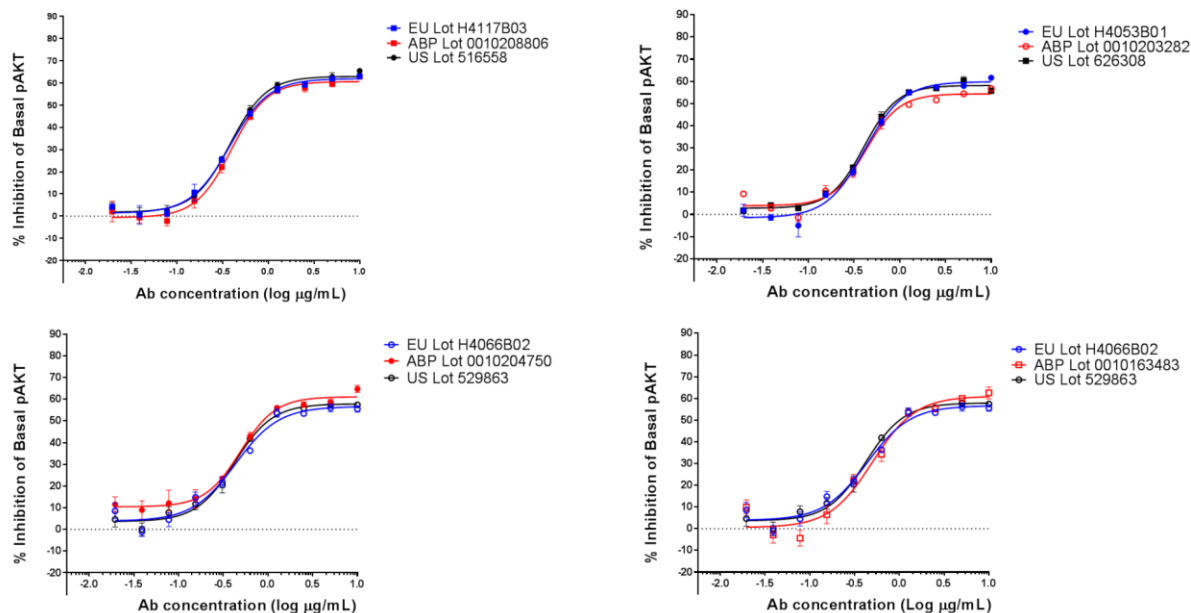
k_a = association rate constant; k_d = dissociation rate constant; K_d = dissociation equilibrium binding constant; recombinant HER2 = human epidermal growth factor receptor 2 extracellular domain, recombinantly expressed

Reviewer Comment: The dissociation equilibrium binding constants for ABP 980 lots all fall within the range of US-licensed Herceptin lots. Based on the known variability of SPR, it is reasonable to conclude that values for the association and dissociation rates constants across all three products would fall well within the expected assay variability. For these reasons, the data support a determination of similarity between ABP 980, US-licensed Herceptin, and EU-approved Herceptin regarding HER2 binding kinetics.

3.2.R.1.8.10 Inhibition of AKT Phosphorylation (4:3:3)

A sandwich immunoassay was developed to evaluate the inhibition of HER2-mediated AKT phosphorylation by ABP 980, US-licensed Herceptin, and EU-approved Herceptin. Briefly, BT-474 cells were first incubated with the titrated antibody samples (ABP 980, US-licensed Herceptin, and EU-approved Herceptin). Then the cell lysate was transferred to MSD plates pre-coated with anti-AKT capture antibody. The MSD plates were subsequently incubated with phosphorylated AKT (Ser473) detection antibody. The levels of phosphorylated AKT in the lysate were measured by an MSD imager. This assay is orthogonal to the potency assay and is considered a Tier 3 for similarity assessment. Four ABP 980 lots, 3 lots each of US-licensed Herceptin and EU-approved Herceptin were tested in one side-by-side experiment. The dose-response profiles from 4 sets of side-by-side comparisons for ABP 980, US-licensed Herceptin, and EU-approved Herceptin lots are shown in Figure 10. Results show the dose-response curves are visually similar between the 3 products.

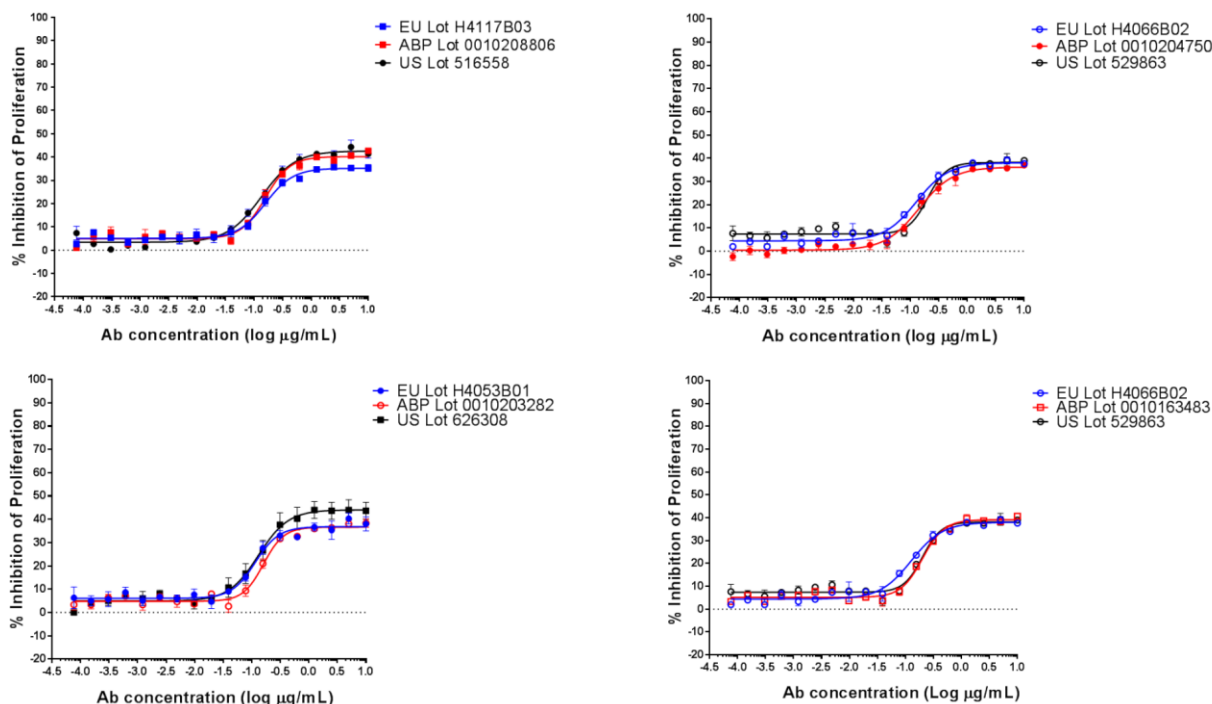
Figure 10. Representative Inhibition of Akt Phosphorylation by ABP 980, Trastuzumab (US), and Trastuzumab (EU) in BT-474 Cells



3.2.R.1.8.11 Inhibition of Proliferation in NCI-N87 Cells (4:3:3)

The inhibition of proliferation of NCI-N87 cells by ABP 980, US-licensed Herceptin, and EU-approved Herceptin was evaluated for similarity assessment. The procedure is similar to the primary potency assay except for the cell line used (NCI-N87 replaced BT-474). This method is orthogonal to the primary potency assay and is considered as a Tier 3 attribute. Four ABP 980 lots, 3 lots each of US-licensed Herceptin and EU-approved Herceptin were tested in one side-by-side experiment. Figure 11 shows the inhibition of proliferation in NCI-N87 cell assay results for the three products.

Figure 11. Trastuzumab (EU), ABP 980, and Trastuzumab (US) Inhibit Ligand-independent Proliferation of NCI-N87 Cells



Reviewer Comment: Data support that ABP 980, US-licensed Herceptin, and EU-approved Herceptin are similar for inhibition of NCI-N87 proliferation.

3.2.R.1.8.12 Inhibition of Proliferation: Synergy with Chemotherapeutic in NCI-N87 Cells (4:3:3)

Trastuzumab is known to enhance the activity of multiple chemotherapeutics (e.g., docetaxel) and is approved for use in the clinic in combination with chemotherapy for breast and gastric cancer. The inhibition of proliferation synergy with docetaxel in NCI-N87 cells was assessed for ABP 980, US-licensed Herceptin, and EU-approved Herceptin. After application of antibody samples and docetaxel to NCI-N87 cells for 120 hours, cells were lysed and the ATP concentration in the lysate was determined using a luminescent plate reader. Growth inhibition was calculated by normalizing growth in treated samples to untreated controls. The synergy scores were calculated from the dose matrices using a Loewe Additivity Model. Four ABP 980 lots, 3 lots each of US-licensed Herceptin and EU-approved Herceptin were tested. Figure 12 shows the inhibition of proliferation by ABP 980, US-licensed Herceptin, and EU-approved Herceptin in the presence and absence of docetaxel (0.003 µM). The dose-response curves for the three products are visually similar. Calculated synergy scores are presented in Table 10.

Figure 12. Comparison of Docetaxel in Combination With Trastuzumab (EU), ABP 980, and Trastuzumab (US) on the Growth of NCI-N87 Cells

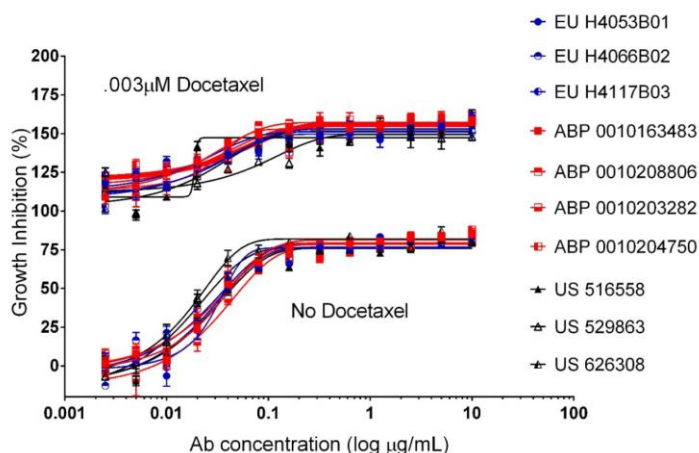


Table 10. Synergy Scores for ABP 980, Trastuzumab (EU), and Trastuzumab (US) in Combination with the Chemotherapeutic Docetaxel

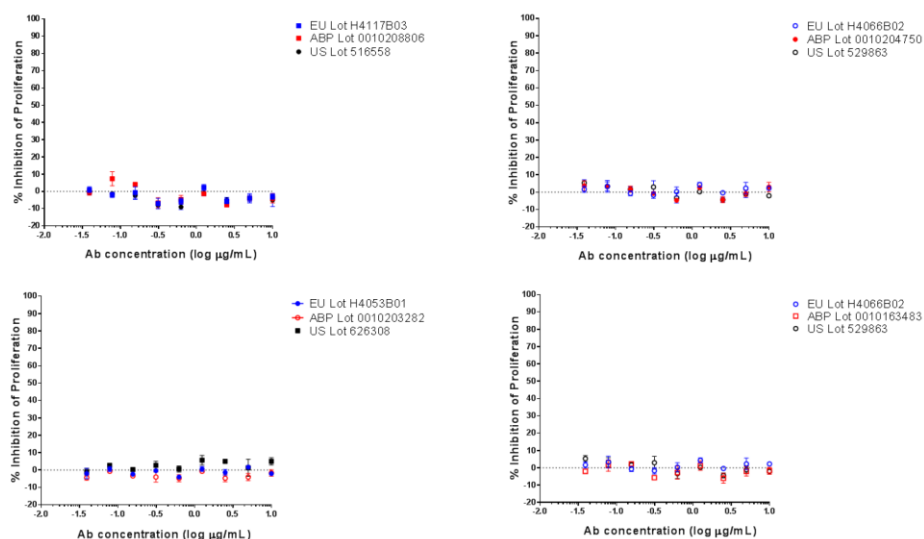
Lot Number	Synergy Score	Lot Number	Synergy Score	Lot Number	Synergy Score
EU H4053B01	17	ABP 0010204750	16	US 516558	18
EU H4066B02	15	ABP 0010203282	17	US 529863	15
EU H4117B03	15	ABP 0010208806	14	US 626308	17
		ABP 0010163483	17		

Reviewer Comment: Regarding synergy with docetaxel on cell growth inhibition, ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin. Additionally, EU-approved Herceptin is similar to US-licensed Herceptin.

3.2.R.1.8.13 Lack of Inhibition of Proliferation in Non-amplified HER2 Cells (4:3:3)

It has been reported that trastuzumab does not inhibit the proliferation of cells with low, non-amplified HER2 expression. A cell based proliferation assay, which is analogous to the inhibition of proliferation in NCI-N87 cells, was developed. In this study, a human breast cancer cell line (MCF7) that expresses low levels of HER2 and does not show amplification of the HER2 gene replaces NCI-N87 cell line. It was performed as an additional characterization study and is considered a Tier 3 assay. Four ABP 980 lots, 3 lots each of US-licensed Herceptin and EU-approved Herceptin were tested in a side-by-side experiment. Figure 13 shows no inhibition of proliferation in MCF7 observed for the three products.

Figure 13. Lack of Inhibition of Proliferation in Non-amplified HER2 Cells by Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: Data support similarity among ABP 980, US-licensed Herceptin, and EU-approved Herceptin regarding lack of inhibition of proliferation in non-amplified HER2 cells.

3.2.R.1.8.14 Lack of Antibody-dependent Cellular Cytotoxicity in HER2 Negative (1:1:1)

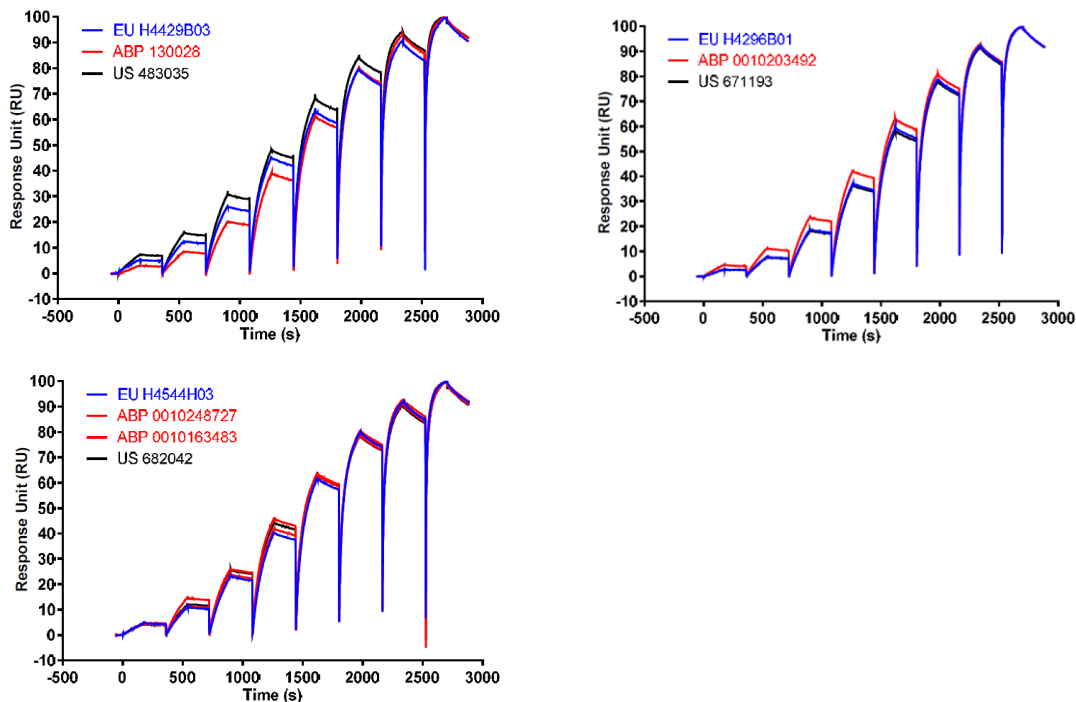
The lack of ADCC in HER2 non-expressing cells was assessed for 1 lot each of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The same ADCC assay was employed except that HER2 non-expressing MDA-MB-468 cells were used as the target cells. No ADCC was observed for ABP 980, US-licensed Herceptin, and EU-approved Herceptin in MDA-MB-468 cells, while the positive control in HCC2218 cells demonstrated ADCC activity. The lack of ADCC activity in HER2 non-expressing cells is considered a Tier 3 attribute and the results are visually similar for the three products.

Reviewer Comment: As expected all three products did not show ADCC activity in HER2 non-expressing MDA-MB-468 cells. Data support the conclusion of high similarity between ABP 980 and US-licensed Herceptin and the adequacy of the analytical component of the scientific bridge to use EU-Approved Herceptin in clinical study.

3.2.R.1.8.15 FcγRIa Binding Analysis (4:3:3)

Binding to the activating, high affinity FcγRIa expressed on macrophages, dendritic cells (DCs), and neutrophils was assessed in a kinetic binding assay using a Biacore T200. In this assay, His-tagged recombinant human FcγRIa is captured by an anti-His antibody on the CM5 Biacore chip. The binding kinetics was determined for each sample in triplicate using a 1:1 kinetic binding model. The binding assay was used as a characterization method and FcγRIa Binding is considered a Tier 3 attribute. Four ABP 980 lots, three lots each of US-licensed Herceptin, and EU-Approved Herceptin were tested in a side-by-side experiment. Three sets of side-by-side overlays are provided below.

Figure 41. FcγRIa Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

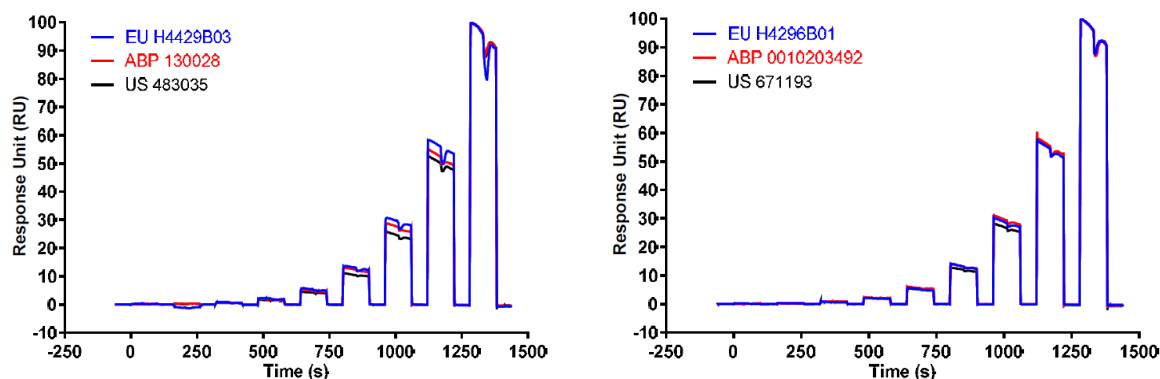


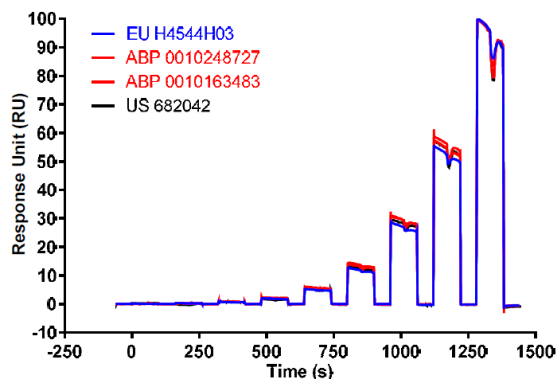
Reviewer Comment: The side-by-side overlays show visibly similar binding patterns for the three products, demonstrating that ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin with respect to their level of FcγRIa binding affinity.

3.2.R.1.8.16 FcγRIIb Binding Analysis (4:3:3)

Binding to FcγRIIb expressed on B cells, macrophages, and dendritic cells was assessed using an SPR assay. This assay is analogous to the FcγRIa binding assay except that the CM5 chip was coated with recombinant human FcγRIIb. FcγRIIb is considered a Tier 3 attribute for similarity assessment. Four ABP 980 lots, three lots each of US-licensed Herceptin, and EU-Approved Herceptin were tested in a side-by-side experiment. Three sets of side-by-side overlays are provided below.

Figure 42. FcγRIIb Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)





Reviewer Comment: The side-by-side overlays show similar Binding patterns for the three products, demonstrating that ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin with respect to their level of FcγRIIb binding affinity.

3.2.R.1.8.17 FcγRIIa (131H) Binding Analysis (16:13:13)

Fc gamma receptor Type IIa (FcγRIIa) is an activating receptor expressed on macrophages, DC, and neutrophils. In this study, a competitive AlphaLISA™ binding assay was used to assess the binding of ABP 980, US-licensed Herceptin, and EU-Approved Herceptin to FcγRIIa (131H). This assay is analogous to the FcγRIIIa (158V) binding assay, except that the acceptor beads are coated with recombinant human FcγRIIa (131H)-GST. Sixteen ABP 980 lots, and thirteen lots each of US-licensed Herceptin, and EU-Approved Herceptin were tested. The applicant noted that “the FcγRIIa binding assay was performed on an expanded number of lots comprised of trastuzumab (US) and trastuzumab (EU) before and after the observed shift in ADCC activity as the underlying glycan changes responsible for that shift could potentially affect binding to FcγRIIa.” The FcγRIIa binding is orthogonal to the ADCP assay and is classified as a Tier 3 attribute. Results are listed below.

Table 22. FcγRIIa Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

Lot Number	Relative Binding to FcγRIIa (131H) (%)	Lot Number	Relative Binding to FcγRIIa (131H) (%)	Lot Number	Relative Binding to FcγRIIa (131H) (%)
EU H0764B01	96	ABP 0010204750	100	US 483035	106
EU H4053B01	106	ABP 0010203282	103	US 495176	106
EU H4066B02	102	ABP 0010208806	94	US 516558	104
EU H4117B03	103	ABP 0010203492	99	US 529863	98
EU H4151B02	103	ABP 0010232325	100	US 569320	104
EU H4176B01	108	ABP 0010235955	101	US 626308	100
EU H4180B02	105	ABP 0010163483	98	US 671193	95
EU H4196B02	103	ABP 0010264945	102	US 3006878	92
EU H4267B06	97	ABP 0010295296	90	US 682042	93
EU H4296B01	97	ABP 0010309515	92	US 680586	88
EU H4429B03	105	ABP 0010309516	92	US 3014299	81
EU H4499H02	86	ABP 0010309517	95	US 3055922	87
EU H4544H03	85	ABP 0010253484	94	US 3072720	82
		ABP 0010262996	98		
		ABP 0010262997	94		
		ABP 0010302656	93		
EU mean	99.7	ABP mean	96.6	US mean	95.1
EU SD	7.3	ABP SD	3.9	US SD	8.9
EU min to max range	85 to 108	ABP min to max range	90 to 103	US min to max range	81 to 106

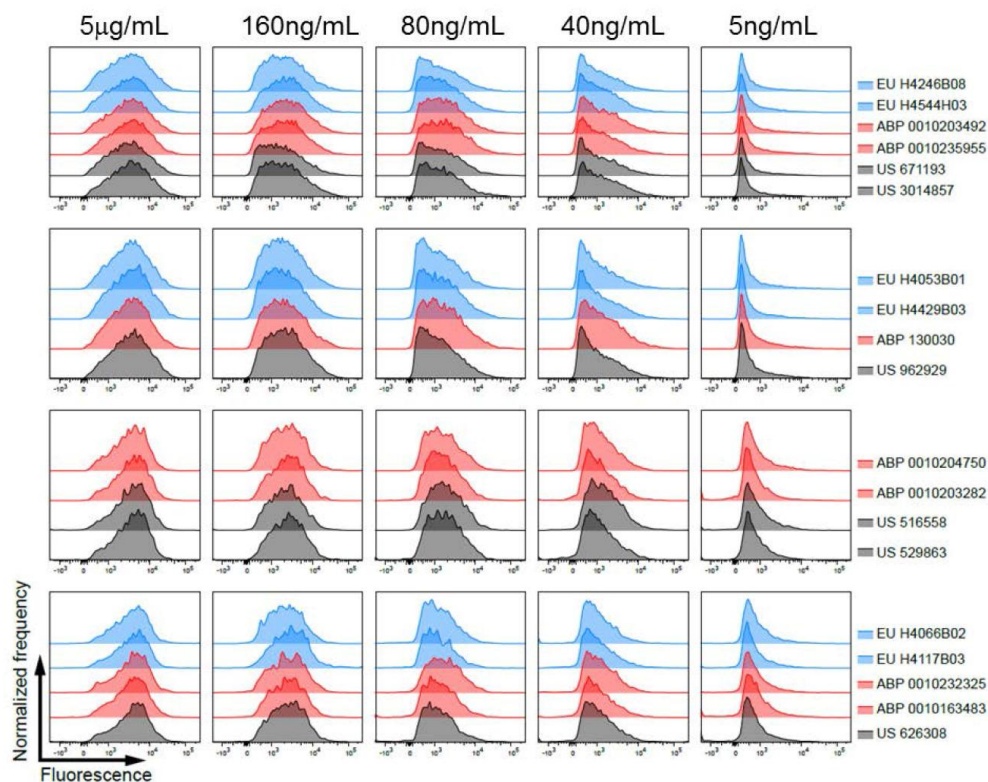
Reviewer Comment: Data demonstrate that ABP 980 is similar to US-licensed Herceptin and EU-approved Herceptin with respect to their level of FcγRIIa binding. Values for ABP 980 fall within the range observed for the US-licensed Herceptin. Additionally, the range of values for EU-approved Herceptin overlap with US-licensed Herceptin with mean values for ABP 980 and EU-approved Herceptin both falling within 1 standard deviation of the mean value for US-licensed Herceptin. For these reasons, data support a determination of high similarity between ABP 980 and US-licensed Herceptin and the adequacy of the scientific bridge for use of EU-Approved Herceptin in clinical study.

3.2.R.1.8.18 Antibody-dependent Cellular Phagocytosis (ADCP) (7:6:6)

It has been reported that trastuzumab induces antibody-dependent cellular phagocytosis (ADCP) through binding to FcγRIIa expressed on macrophages and dendritic cells. An ADCP assay was developed as an additional characterization method and is considered a Tier 3 assay. For the similarity assessment, the ADCP data were generated by testing seven ABP 980 lots, six lots each of US-licensed Herceptin and EU-approved Herceptin lots in four side-by-side experiments. The applicant noted that “the ADCP assay was comprised of trastuzumab (US) and trastuzumab (EU) lots before and after the observed shift in ADCC activity as the underlying glycan changes responsible for that shift could potentially affect ADCP activity.” In this assay, SKBR-3 cells, that stably express high levels of HER2 on cell surface, are used as target cells;

while human PBMC cells are used as effector cells. Fluorescence labeled SKBR-3 cells, PBMC cells, and antibody samples ranging from 5 µg/mL to 2.441 ng/mL are incubated together for 2.5 hours. Fluorescence positive macrophage cells are collected by FACS and analyzed using FlowJo software. Results are presented below for visual comparison and are considered similar.

Figure 40. ADCP Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The ADCP results for ABP 980, US-licensed Herceptin, and EU-approved Herceptin show superimposable FACS profiles, thus supporting similarity of ABP 980, US-licensed Herceptin, and EU-approved Herceptin with respect to ADCP.

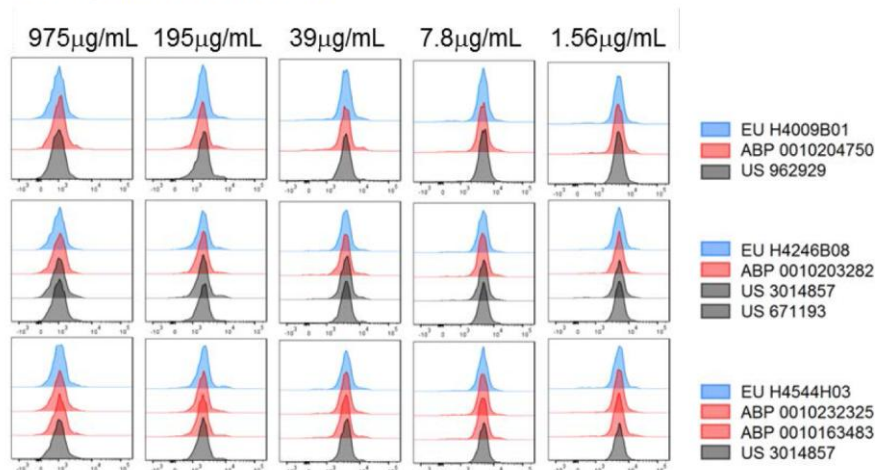
3.2.R.1.8.19 FcγR Binding on Primary Macrophages (4:4:3)

Macrophages express multiple Fcγ receptors (FcγRs) including FcγRIa, FcγRIIa, and FcγRIIb. Binding to primary macrophages was evaluated for ABP 980, US-licensed Herceptin, and EU-approved Herceptin using a cell based competitive assay. This assay is supportive of the individual FcγR binding assays and is considered a Tier 3 assay for analytical similarity assessment. Data were generated by testing four ABP 980 lots, four US-licensed Herceptin lots, and three EU-approved Herceptin lots. In this study, each sample was serially diluted and mixed with a fluorescence labeled ABP 980 reference standard (200 µg/mL), and then incubated with human PBMC cells for 1 hour. Fluorescence positive cells were detected by FACS and histograms were generated by FlowJo data analysis. Given FcγRIIa has 2 allelic variants (131H and 131R), the human PBMC cells derived from one 131 R/R donor and one 131 H/R donor were used respectively for side-by-side testing. Side-by-side histogram overlays from 2

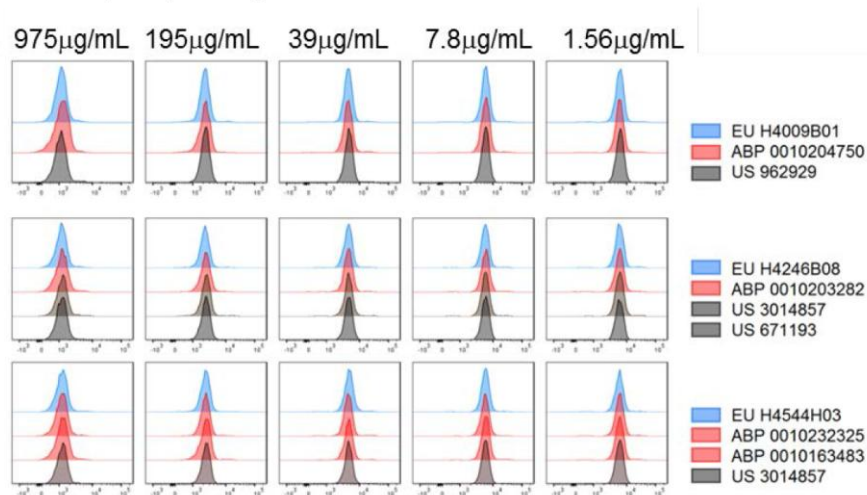
different genotyped donors are shown in figure 44 below. The results for ABP 980, US-licensed Herceptin, and EU-approved Herceptin are similar.

Figure 44. FcγR Binding on Primary Macrophages for Trastuzumab (EU), ABP 980, and Trastuzumab (US)

PBMCs-FcγRIIa (131 R/R) donor



PBMCs-FcγRIIa (131 H/R) donor

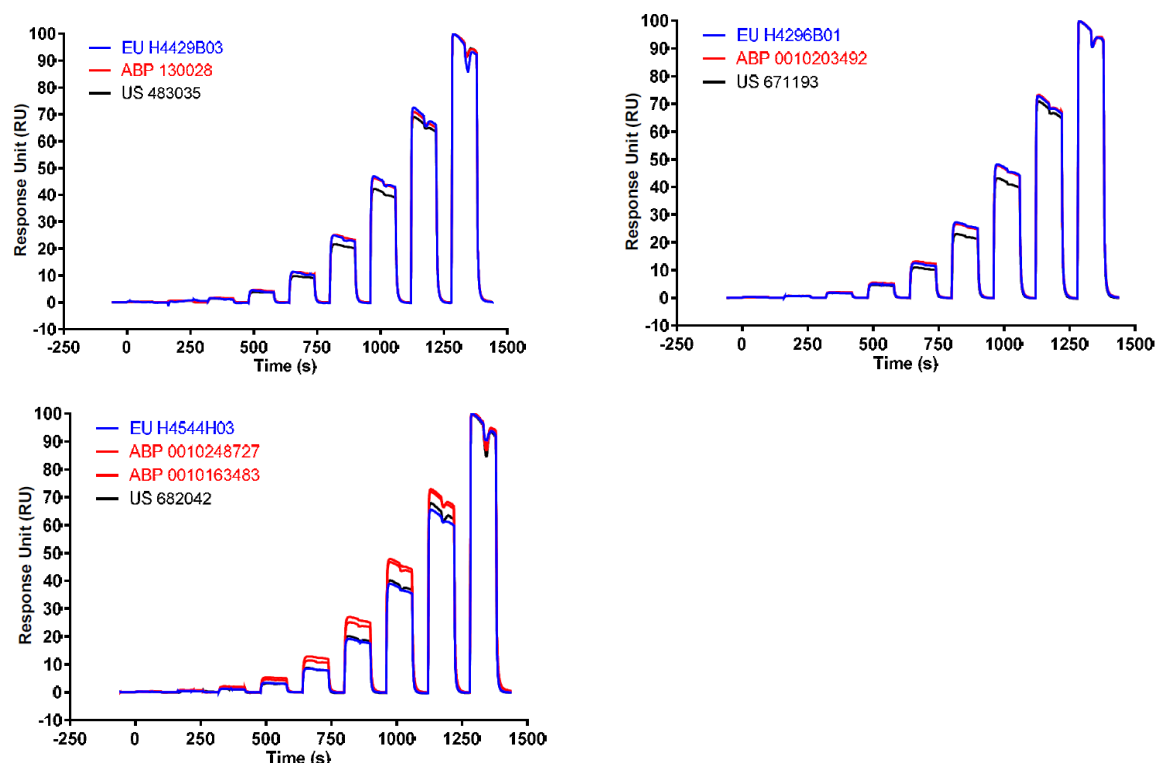


Reviewer Comment: The FcγR binding on primary macrophages results are similar for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

3.2.R.1.8.20 FcγRIIIb Binding (4:3:3)

FcγRIIIb binding was assessed for ABP 980, US-licensed Herceptin, and EU-approved Herceptin using a SPR assay, which is analogous to the FcγRIa binding assay (see the FcγRIa binding section above) except that the CM5 chip was coated with recombinant human FcγRIIIb. Four ABP 980 lots, 3 lots each of US-licensed Herceptin, and EU-approved Herceptin were tested in a side-by-side experiment. Side-by-side overlays for all lots tested are visually similar.

Figure 45. FcγRIIIb Binding Results for Trastuzumab (EU), ABP 980, and Trastuzumab (US)



Reviewer Comment: The FcγRIIIb binding results are similar for ABP 980, US-licensed Herceptin, and EU-approved Herceptin.

5.3.1.4 Immunogenicity Assays

The below sections on immunogenicity assays were written by Chih-Jung Hsu.

The sponsor developed a two-tiered immunogenicity assay system to detect and characterize anti-drug antibody (ADA) responses elicited in patients by ABP 980 administration. The two-tiered immunogenicity assessment consists of (1) electrochemiluminescence (ECL)-based screening and confirmatory (described as specificity in the submission) assays and (2) a non-cell based competitive ligand binding neutralization assay. For each assay, the first review bullet point focuses on assay principle and method design. The second review bullet point summarizes the method validation parameters including assay sensitivity, assay cut-point, and drug interference.

(1) Screening and confirmatory (specificity) assay

➤ Assay principle and method design

The assay procedure is referred to MET-003394 and the method validation report is referred to MVR-000469. Samples in 5% serum are first treated with 300 mM acetic acid to dissociate the pre-formed ADA-drug complex. Acid-treated samples are incubated with biotinylated ABP 980 and ruthenylated ABP 980 to allow complex formation. The incubated sample is then transferred to a 96-well plate coated with avidin. The presence of ADA immobilizes the soluble ABP 980 complex (biotinylated ABP 980 and ruthenylated ABP 980) to the plate surface. After incubation and removal of unbound molecules, the ECL signal is detected by the Meso Scale Discovery

(MSD) plate reader. If the signal to noise (S/N) is greater than the screening cut-point of 1.15, the sample is subjected to the confirmatory (specificity) assay.

To confirm the screening positives, an excess amount of unlabeled ABP 980 is added to the sample mixture to compete with the biotinylated ABP 980. When ADAs are saturated by the competitive unlabeled ABP 980, the surface-bound ADA is reduced as well as surface-bound ABP 980 complex, resulting in a decrease in the final ECL readout. The sample is confirmed as ADA positive if the ECL depletion ratio is greater than 26%.

Reviewer comments:

The principle of screening assay is based on the molecular binding between ABP 980 and ADA. The complexes of ADA and ABP 980 (including biotinylated ABP 980 and ruthenylated ABP 980) are anchored to the plate surface via specific biotin-avidin interaction. An electrical current is initiated across the plate to induce oxidation-reduction reaction involving ruthenium and tripropylamine. The amount of surface-bound ADA is proportional to the ECL intensity.

The confirmatory assay is based on the competitive binding. Excess unlabeled ABP 980 competes with biotinylated ABP 980 and ruthenylated ABP 980 to reduce the surface-bound ADA. The use of two-tiered approach meets the assay design recommendations in Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (CDER, 2016). The proposed assay design is suitable to screen and confirm the presence of ADA in patient samples. Of note, the confirmatory assay is described as 'specificity' assay in the submission.

➤ The method validation parameters

The critical validation results are retrieved from MVR-000469 and summarized in the reviewer table below. The other validation results not included in the table, such as materials, reagents, instrument, software, sample stability, and serum factor can be found in MVR-000469.

Validation experiment	Parameters	Results
Population	# of donors tested	50
	# of samples tested	200
Screen Assay Cut Point (ACP)	Signal to noise (S/N)	> 1.15 (Table 3 and Fig. 3) [‡]
Confirmatory Depletion Cut Point (DCP) Depletion % = 100% - (drug treated S/N / non-treated S/N)%	% S/N depletion	> 26% (Table 3 and Fig. 4) [‡]
Screen Assay Sensitivity	Concentration	19 ng/mL (Table 4 and Fig. 5) [‡]
Confirmatory Assay Sensitivity	Concentration	53 ng/mL (Table 5 and Fig. 6) [‡]
Low Positive Control (LPC)	Concentration	100 ng/mL in PNHS
High Positive Control (HPC)	Concentration	500 ng/mL in PNHS
Unlabeled ABP 980 used in Confirmatory Assay	Concentration	100 µg/mL
Lower Limit of Reliable Detection (LLRD)	Concentration	120 ng/mL (Table 11) [‡]
Hook Effect	Observed	Not observed up to 100 µg/mL (Table 6 and Fig. 7) [‡]
	Concentration	
Screening Assay Drug Tolerance	Concentration	At LPC and LLRD: tolerance of 50 µg/mL ABP 980 At HPC: tolerance of 250 µg/mL ABP 980 (Table 13) [‡]
Confirmatory Assay Drug Tolerance	Concentration	At LPC and LLRD: tolerance of 20 µg/mL ABP 980 At HPC: tolerance of 100 µg/mL ABP 980 (Table 13) [‡]

Intra-Assay Precision CV [†] (n = 4, control runs in quadruplicates)	ECL CV [†]	NC (Negative control): 13% LPC: 3% HPC: 6% (Table 8)*
Inter-Assay Precision CV [†] (n = 34 assays in total)	ECL CV [†]	NC: 15% LPC: 14% HPC: 23% (Table 7)*

[†]Coefficient of variation

*Provided in MVR-000469, not included in the review

The resource and usage of critical reagents used in the screening assay is summarized in the reviewer table below.

Reagents	Usage	Resource
Pooled normal human serum (PNHS)	Negative control, background response	Commercial product from (b) (4)
Anti-ABP 980 polyclonal antibody	Positive control	Immunization of ABP 980 into rabbits. In-house prepared
biotinylated ABP 980	Used to react with anti-ABP 980 antibody	In-house prepared
Ruthenylated ABP 980	Used to react with anti-ABP 980 antibody and generate ECL signal	In-house prepared

Reviewer comments:

• **Screening assay cut point (ACP) and confirmatory depletion cut point (DCP):** the ACP and DCP are established statistically using data collected from 50 human serum samples from a cancer (breast or colorectal) donor population. The data were analyzed by 2 analysts, 2 MSD instruments, and at 2 sites. A fixed ACP of $S/N > 1.15$ is established by statistical analysis with an upper bound of one-side 95% prediction interval of S/N values. With the proposed ACP, 95.5% of the donor samples exhibit $S/N \leq 1.15$. A fixed DCP of $> 26\%$ is established based on statistical analysis with an upper bound of one-side 99% prediction interval of percent ratio of S/N depletion values. With the proposed fixed DCP, all donor samples exhibit responses $\leq$ DCP.

The number of analyzed samples (n = 50) is statistically sufficient. Assay reproducibility can be demonstrated by variables in operators, instruments, and testing sites. The respective prediction intervals of 95% and 99% are appropriate to minimize the false-positive population and to allow the detection of spiked positive controls at screening. Overall, the establishment of ACP and DCP is acceptable.

• **Assay sensitivity:** the sponsor defines the assay sensitivity as the lowest ADA concentration that meets ACP or DCP. Rabbit ADA samples with concentrations ranging from 5 to 640 ng/mL were spiked into pooled normal human serum (PNHS). The dose response curves were fitted to a non-linear regression model to obtain the lowest ADA concentration that meets ACP or DCP. The reported assay sensitivities are 19 ng/mL for screening and 53 ng/mL for confirmatory. Both are well within the recommended range of 100 ng/mL in Draft Guidance (CDER, 2016). Because the spiking range is wide enough to conduct a logistic fit, the determination of assay sensitivity is statistically supported.

• **Drug tolerance:** the sponsor defines the drug tolerance in the screening assay as the ABP 980 concentration that still exhibits S/N value above ACP in the presence of drug. The drug tolerance in the confirmatory assay is defined as the ABP 980 concentration that will exhibit S/N value above both ACP and DCP. The determination of drug tolerance is based on spiking 0 - 500 μ g/mL ABP 980 into the negative control, LPC, LLRD, and HPC samples. In section 2.7.2 – summary of clinical pharmacology studies, the reported trough ABP 980 concentrations vary from 33.0 – 44.1 μ g/mL. The resulting tolerance limits range from 50 μ g/mL to 250 μ g/mL and are well above the

reported trough concentrations. Therefore, the drug tolerance limits are adequate to detect ADA in the presence of drug at the trough level.

- **System suitability controls:** the sponsor determined a low positive control (LPC), a high positive control (HPC), and assay control precision to establish system suitability. LPC is the lowest positive control concentration that is statistically determined to allow 99% of assay results passing the combined ACP and DCP. Based on the statistical analysis, the LPC range is 92 – 127 ng/mL and 100 ng/mL is selected. HPC is selected to exhibit about 5 times S/N of ACP. Given ACP = 1.15 S/N, 500 ng/mL is selected as HPC. The selection of 100 ng/mL as LPC is close but higher than the confirmatory assay sensitivity of 53 ng/mL. The justification of allowing 99% of assay results fulfilling the combination of ACP and DCP is acceptable to reduce the chance of false-positive results. For HPC, a concentration exhibits the S/N value 5 times higher than ACP is sufficient to reduce the chance of false-negative results. Based on the assessments above, I agree with the establishment of LPC and HPC.

Regarding assay control precision, assay precision is determined by the calculation of intra- and inter-assay %CV of NC, LPC, and HPC samples. The proposed precision acceptance criteria of $\leq 20\%$ meet the recommended 20% CV in the Draft Guidance (CDER, 2016). Intra-assay study is assessed by quadruplicates and inter-assay study is assessed by 2 plate lots, 2 buffer lots, 2 instruments, 17 days, 2 analysts and 2 sites. Both studies are suitable to support the control precision. Along with the LPC and HPC, the assay suitability can be demonstrated by a statistically-established positive control range with a robust assay precision. Overall, the assay system suitability is validated.

- **Critical reagents:** PNHS (commercial product) is used in spiking studies to serve as a matrix background or negative control. To mimic the reasonable serum condition in spiking studies, the use of PNHS is adequate. Biotinylated ABP 980 and Ruthenylated ABP 980 are both characterized by SE-HPLC and Biacore. The submitted figures 1 and 2 and tables 1 and 2 in MVR-000469 support the bioactivities of Biotinylated ABP 980 and Ruthenylated ABP 980.

In addition, for positive control, samples are stable for up to 5 freeze/thaw cycles, for 24 hours at room temperature, and for 3 days at 2 – 8 °C. The stability duration is sufficient to conduct the assay procedure.

(2) Neutralization assay

➤ Assay principle and method design

The bioanalytical assay used to detect the neutralizing ADA is referred to MET-3419, ‘A Target Binding Assay to Detect Neutralizing Antibodies against ABP 980 in Human Serum’. The assay validation is referred to MVR-000470, ‘Analytical method validation report for a target binding assay to detect neutralizing antibodies against ABP 980 in human serum’.

Neutralization assays evaluate ADA for neutralizing activity to block ABP 980 binding to Her2/ErbB2. This target-binding assay is conducted by a fluorescence-based competitive binding method. Briefly, samples in 5% human serum are first incubated with biotinylated ABP 980 to allow complex formation. The incubated sample is then transferred to a 96-well plate coated with recombinant human Her2/ErbB2, the binding target of ABP 980. After removal of unbound molecules, streptavidin conjugated with europium is added to the plate and incubated. After washing the plate, the fluorescence enhancement solution (Dissociation – Enhanced Lanthanide Fluorescent Immunoassay, DELFIA) is added and the fluorescence signal is measured by EnVision plate reader. If neutralizing ADAs are present in the sample, the fluorescence signal will be reduced due to the binding of neutralizing ADA to biotinylated ABP 980.

To confirm the positive results, an excess amount of unlabeled ABP 980 is added to the sample mixture to compete with the biotinylated ABP 980. With neutralizing ADAs saturated by the competitive unlabeled ABP 980, the available amount of neutralizing ADAs is reduced, resulting in an increase in the final fluorescence readout. The established confirmatory assay cut point is > 2.00 . The assay parameters are summarized in the table below.

Reviewer comments:

The principle of neutralization assay is based on the competitive binding between ABP 980 with neutralizing ADA and with Her2/ErbB2. The confirmatory step is established by adding excess unlabeled ABP 980 to saturate soluble neutralizing ADA, resulting in an increase in final readout.

The use of ABP 980 binding target, Her2/ErbB2, to compete with the ADA is suitable to characterize ADA for neutralizing activity against HER2 binding of ABP 980, which reflects the primary mechanism of action. Therefore, proposed neutralization assay is acceptable to assess neutralizing ADA.

➤ The method validation parameters

The critical validation results are retrieved from MVR-000470 and summarized in the reviewer table below. The other validation results not included in the table, such as materials, reagents, instrument, software, and sample stability can be found in MVR-000470.

Validation Parameters	Validation Results
Drug Control (DC) in Screening Assay	35 ng/mL biotinylated ABP 980
Positive Control (PC) in Screening Assay	35 ng/mL biotinylated ABP 980 + 45 ng/mL anti-trastuzumab
Positive Control (PC) in Confirmatory Assay	35 ng/mL biotinylated ABP 980 + 45 ng/mL anti-trastuzumab + 0.11, 0.33, or 1 µg/mL ABP 980
Confirmatory Assay Value (CAV)	Mean confirmatory sample or control tested at a non-zero ABP 980 concentration / mean of the corresponding sample or control tested at zero ABP 980 concentration
Confirmatory Assay Cut Point	2.0
Assay Sensitivity	700 ng/mL (Figure 2) [‡]
Unlabeled ABP 980 used in Confirmatory Assay	0.11, 0.33, or 1 µg/mL ABP 980
Lower Limit of Reliable Detection (LLRD)	0.9 µg/mL
Upper Limit of Reliable Detection (ULRD)	20 µg/mL
Screen Assay Drug Tolerance	0.296 µg/mL ABP 980 at LLRD 5.0 µg/mL ABP 980 at ULRD (Figure 12) [‡]
DC/PC for system suitability	≥ 2.00 (Figure 1) [‡]

[‡]Provided in MVR-000470, not included in the review

Reviewer comments:

- The validation study to support the establishment of assay cut point > 2.0 is summarized in the reviewer table below.

Table. Summary of validation results regarding the confirmatory assay cut point of 2.00

	Negative Control (unspiked)	Positive Control (spiked with LLRD 0.9 µg/mL and ULRD 20 µg/mL of anti-trastuzumab antibody)	Drug Control (spiked with 1 µg/mL and 10 µg/mL of ABP 980)
Diseased population (21 donors)	All negative (Fig. 4) [‡]	At LLRD: all positive (Fig. 5) [‡] At ULRD: 20/21 positive (Fig. 6) [‡]	All negative (Fig. 7) [‡]
Healthy population (20 donors)	All negative (Fig. 8) [‡]	At LLRD: all positive (Fig. 9) [‡] At ULRD: 19/20 positive (Fig. 10) [‡]	All negative (Fig. 11) [‡]

[‡]Provided in MVR-000470, not included in the review

The assay cut point is established at the low concentration of 0.9 µg/mL and high concentration of 20 µg/mL anti-trastuzumab antibody. This screening range is wide enough to simulate the possible meaningful neutralizing ADA

level and is reasonable to evaluate the detection linearity. The sizes of population from both healthy and diseased groups are statistically sufficient. No false-positive results are reported in the negative control and drug control (1 µg/mL and 10 µg/mL of ABP 980). Regarding positive control, there is only one donor sample that does not pass the proposed cut point in both populations, resulting in 5% false negative at ULRD. Taken together with 0% false negative at LLRD, the assay cut point of > 2.00 is acceptable.

- **Assay sensitivity:** neat pooled human normal serum was spiked with 0.1 to 1.0 µg/mL anti-trastuzumab antibody positive control in the presence of 0.11, 0.33, or 1.0 µg/mL of unlabeled ABP. The assay sensitivity is determined as the lowest concentration at which a sample exhibits CAV > 2.00. Because the spiking range is sufficient, the assay sensitivity can be supported by the validation study.
- **Drug tolerance:** determination of drug tolerance is based on spiking ABP 980 (0.059 - 25.0 µg/mL) into the negative control and positive control samples (0.9 and 20 µg/mL anti-trastuzumab). The highest ABP concentration that exhibits a CAV value greater than 2.00 is defined as the drug tolerance limit. Because the number of studies (n = 3), ABP 980 spiking range, and positive control range are all statistically sufficient, the establishment of drug tolerance limit is acceptable.
- **System suitability:** DC/PC is calculated from each plate and used to assess system suitability. For screening and confirmatory assay, the system suitability acceptance criterion is DC/PC ≥ 2.00. Based on the data provided in Table 1 in MRV-000470, the ratio of DC/PC varies from 3.71 to 9.26 in 32 samples. The number of studies (n = 32) and reported DC/PC values are statistically sufficient to support the proposed system suitability acceptance limit.
- In Feb 8, 2018 Establishment Inspection Report (EIR) drafted by Office of Study Integrity and Surveillance (OSIS), a deficiency of excluding failed validation runs in precision assessment is documented in observation #2. OSIS inspector states "Inclusion of failed runs in global assay precision resulted in assay precision not meeting the acceptance criteria". The sponsor acknowledges that four failed runs were not included in precision assessment and reports that three of the four failed runs are due to technical error and therefore, should not be considered in precision calculation.

In Feb 14, 2018 response to OSIS comments on observation 2, the sponsor provided raw data for the three failed runs (table below, derived from Table 3 in the response).

Assay Purpose	Date	Assay No.	Plate No.	Pass/Failed	Reason for Failed Assay	DC/PC	PC _{1.00} /PC	PC _{0.33} /PC	PC _{0.11} /PC
Other serum Interference	28-Oct-2014	23	1	Fail	Technical Error	0.00	0.67	1.73	3.36
Other serum Interference	28-Oct-2014	23	2	Fail	Technical Error	0.00	0.65	1.71	3.36
Other serum Interference	28-Oct-2014	23	3	Fail	Technical Error	0.00	0.62	1.64	3.23

Three "Technical Error" runs exhibit results of 0.00 in DC/PC. These three values are significantly deviated from other validation results in the same table, all passing suitability criterion of DC/PC > 2.00. Because the readout of 0.00 is not a scientific meaningful measurement and does not meet the suitability criterion, these data are not suitable for the validation study. These three "Technical Error" runs were all conducted on the same date (10/28/2014) within the same experiment (Assay No. 23) but using three different plates. No other validation runs showing 0.00 in DC/PC are observed in the reported results. Based on the assessments above, I agree that these three runs can be interpreted as operation error and they are not suitable for assay precision assessment.

- The summary of immunogenicity assay results, study subjects, population sizes, and sampling times for study 20130119 and study 20120283 is provided in the table made by the reviewer.

	Study 20130119	Study 20120283	Reviewer comments
Purpose	PK similarity study	Clinical similarity (efficacy and safety) study	N.A.

<i>Subject</i>	<i>Healthy male volunteers</i>	<i>Female subjects with HER2-positive early breast cancer</i>	<i>N.A.</i>
<i>Population size</i>	<i>118 (64 exposed to ABP 980, 46 to trastuzumab, and 8 to placebo)</i>	<i>725 (364 exposed to ABP 980 and 361 exposed to trastuzumab)</i>	<i>N.A.</i>
<i>Collection times</i>	<i>Day 1 (pre-dose) and day 64 (End-of-Study, EOS day)</i>	<i>Day 1 and day 9 in neoadjuvant phase; day 10, day 14, and day 18 in adjuvant phase; day 23 at End-of-Treatment (EOT) or EOS visit</i>	<i>In Table 14-9.10 on page 467 in section 5.3.3.1 – Clinical Study Report 20130119 – CSR 20130119 – Report Body, the average half-time ($t_{1/2}$) of ABP 980 is 169.408 hours (about 7 days) in 50 healthy volunteers. The sampling times in both studies are well beyond ABP $t_{1/2}$. The samples collected on day 1 (pre-dose) used as the baseline value to assess ABP 980 immunogenicity are acceptable. The drug tolerance levels determined during assay validation support assay capability to detect ADA in samples collected at these times.</i>
<i>% screened positive for ADA[†]</i>	<i>0</i>	<i>0.6% (2 subjects) for ABP 980 and 1.4% (5 subjects) for trastuzumab control</i>	<i>In Study 20120283, ADA positive results are observed in both ABP 980 and trastuzumab arms at a similar rate, supporting the assay adequacy between different treatment groups. The two screen positives for ABP 980 are transient results as the subjects exhibit negative results at the last test time point. Three subjects (0.8%) are observed as false-positive in trastuzumab control in Study 20120283. Given by the statistical prediction of 5% false positive, this rate is acceptable. Overall, the low immunogenic response elicited by trastuzumab in both studies is consistent with published literature.</i>
<i>% confirmed positive for ADA[†]</i>	<i>0</i>	<i>0.6% (2 subjects) for ABP 980 and 0.6% (2 subjects) for trastuzumab control</i>	
<i>% neutralizing ADA[†]</i>	<i>0</i>	<i>0</i>	

[†]Data are retrieved from section 2.7.2 – Summary of Clinical Pharmaceutical Studies



Chen
Sun

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Patrick
Lynch

Digitally signed by Patrick Lynch
Date: 5/23/2018 12:04:47PM
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Chih-Jung (CJ)
Hsu

Digitally signed by Chih-Jung (CJ) Hsu
Date: 5/23/2018 12:30:06PM
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Recommendation: Complete Response

BLA Number: 761073 Office of Product Quality Application Team Lead Review

Review Date: May 22, 2018

Drug Name/Dosage Form	Kanjinti (trastuzumab-anns)/ for injection
Strength/Potency	420 mg/vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indications	Treatment of HER2 overexpressing breast cancer Treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Applicant/Sponsor	Amgen, Inc.

Product Overview

Kanjinti (trastuzumab-anns) is a proposed biosimilar to US-licensed Herceptin. Kanjinti is a humanized IgG1κ monoclonal antibody that binds human epidermal growth factor receptor 2 (HER2). A proposed mechanism of action is inhibition of ligand-independent HER2 signaling, which in turn inhibits the proliferation of tumor cells that overexpress HER2. A second proposed mechanism of action is antibody-dependent cellular cytotoxicity (ADCC) mediated through concomitant binding to HER2 and Fcγ receptors on the surface of immune system effector cells, which leads to anti-tumor immune responses. The drug substance is produced by recombinant DNA technology in cultures of Chinese Hamster Ovary cells. The final drug product is supplied in vials as a white to pale yellow lyophilized powder for reconstitution with bacteriostatic water for injection (bWFI) or sterile water for injection (sWFI). Kanjinti drug product is formulated in 4.2 mM L-histidine, 51 mM α,α-trehalose, 0.008% (w/v) polysorbate 20 at pH 6 (b) (4). The formulation (b) (4) the same as US-licensed Herceptin (trastuzumab) (hereinafter referred to as US-Herceptin).

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Chen Sun	OPQ/OBP/DBRRII
Analytical Similarity	Chen Sun	OPQ/OBP/DBRRII
Drug Product	Chih-Jung Hsu	OPQ/OBP/DBRRII
Immunogenicity Assays	Chih-Jung Hsu	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facilities	Wayne Seifert	OPQ/OPF/DIA
Facilities Team Lead	Zhihao Peter Qui	OPQ/OPF/DIA
Microbiology Drug Substance	Kathleen Jones	OPQ/OPF/DMA
Microbiology Drug Product	Jessica Hankins	OPQ/OPF/DMA

Microbiology QAL	Reyes Candau-Chacon	OPQ/OPF/DMA
Application Technical Lead	Patrick Lynch	OPQ/OBP/DBRRII
Tertiary Reviewer for OBP	Howard Anderson	OPQ/OBP/DBRRII
RBPM	Keith Olin	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Amy Tilley	OND/OHOP/DOP1
Cross-disciplinary Team Lead	Laleh Amiri Kordestani	OND/OHOP/DOP1
Medical Officer	Jennifer Gao, Lynn Howie	OND/OHOP/DOP1
Pharm/Tox	Kimberly Ringgold/Todd Palmby (TL)	OND/OHOP/DHOT
Clinical Pharmacology	Olanrewaju Okusanya/Sarah Schrieber (TL)	OTS/OCP
Statistics	Joyce Cheng/Shenghui Tang (TL)	OTS/OB/DBV
CMC Statistics	Yu-Yi Hsu/ Meiyu Shen (TL)	OTS/OB/DBIV

1. Names:

- a. Proprietary Name: Kanjinti
- b. Trade Name: Kanjinti
- c. Non-Proprietary: Trastuzumab-anns

Submissions Reviewed:

Submission(s) Reviewed (OPQ office)	Document Date
STN 761073/1	July 28, 2017
STN 761073/3 (OPF)	August 31, 2017
STN 761073/5 (OPF)	September 21, 2017
STN 761073/8 (OPF)	October 24, 2017
STN 761073/9 (OPF)	October 30, 2017
STN 761073/12 (OBP, OPF)	November 3, 2017
STN 761073/15 (OBP)	December 8, 2017
STN 761073/18 (OPF)	January 18, 2018
STN 761073/19 (OBP)	January 24, 2018
STN 761073/20 (OBP)	February 14, 2018
STN 761073/21 (OPF)	February 20, 2018
STN 761073/22 (OBP)	February 21, 2018
STN 761073/23 (OBP)	February 26, 2018
STN 761073/24 (OBP)	March 5, 2018
STN 761073/25 (OPF)	March 7, 2018
STN 761073/26 (OBP)	March 16, 2018
STN 761073/28 (OPF)	March 23, 2018
STN 761073/29 (OBP)	March 26, 2018
STN 761073/30 (OPF)	March 29, 2018
STN 761073/31 (OBP, OPF)	April 4, 2018
STN 761073/33 (OPF)	April 11, 2018

STN 761073/34 (OPF)	April 13, 2018
STN 761073/36 (OBP, OPF)	May 14, 2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²
(b) (4)	III	(b) (4)	(b) (4)	3	N/A
	III			3	N/A
	III			3	N/A
	III			2	2
	V			2	2

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

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

B. Other documents: IND 115424

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

This application will not be approved during this review cycle due to drug product facility deficiencies. The Division of Inspectional Assessment, OPF, OPQ is recommending that the application not be approved due to deficiencies related to CGMP that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug product manufacturing facility (b) (4) (b) (4)). The specific deficiencies are discussed in the OPF primary review. From a product quality perspective, the Office of Biotechnology Products, OPQ, CDER and from a microbial perspective OPF/DMA do not note any product quality deficiencies that would preclude approval of BLA 761073 for Kanjinti manufactured by Amgen, Inc. at this time. The analytical similarity data submitted in this application demonstrate that Kanjinti is highly similar to US-Herceptin. A sufficient analytical component of the three-way scientific bridge was established to support the use of EU-approved Herceptin (EU-Herceptin) as a comparator in clinical trials supporting this application. However, based on observations made during PLI of the drug product manufacturing facility, the information provided in support of this application are not adequate to support the conclusion that the manufacture of Kanjinti is well-controlled and leads to a product that is pure and potent. Because the application will not be approved in this cycle, remaining product quality issues that are not approvability issues are listed in the summary of additional comments below. These comments will be communicated to the sponsor in the FDA Complete Response (CR) letter. If manufacturing changes are made before the sponsor submits their responses to the CR deficiency, additional review may be needed during the next review cycle.

The original OPQ Application Team Lead (ATL) review that recommended approval of the application pending final determinations of the compliance status of the (b) (4) drug substance manufacturing facility and the (b) (4) drug product manufacturing facility was completed and signed on April 16, 2018 in Panarama. The original ATL review was updated with this review to incorporate f the Office of Chief Counsel comments and to update the outcomes of ongoing inspectional assessments. This review reflects the final OPQ ATL review and recommendation.

B. Summary of Complete Response Issues (provided by OPF/DIA):

1. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

C. Summary of Additional Comments to be Provided to the Sponsor in the Complete Response Letter (provided by OBP and OPF/DMA):

1. Implement a FcγRIIIa binding test on drug substance release specification and submit a proposal for the FcγRIIIa binding drug substance release specification.
2. Conduct additional characterization to further understand the impact of drug product manufacturing and stability conditions on Fc functions, to inform the need to implement FcγRIIIa binding test on drug product release testing and/or stability. Submit results of the data evaluation and the proposed overall control strategy.
3. (b) (4) were not included for (b) (4). Provide (b) (4) sterilization validation information for the (b) (4) (b) (4) in section 3.2.P.3.5 of the BLA.
4. Media fill simulations to support the ABP 980 (b) (4) did not include the (b) (4) (b) (4) Perform media fill simulations that include (b) (4) (b) (4) (b) (4) (b) (4)
5. The (b) (4) validation data provided in the BLA did not include (b) (4) (b) (4) (b) (4) (b) (4) in section 3.2.P.3.5 of the BLA.
6. The ABP 980 manufacturing process does not include (b) (4) (b) (4). Implement the necessary equipment modifications to designate the (b) (4) (b) (4) (b) (4)

D. Benefit/Risk Considerations:

Kanjinti (trastuzumab-anns) is a proposed biosimilar to US-Herceptin (trastuzumab) for treatment of HER2 overexpressing breast cancer and gastric cancer. Trastuzumab inhibits proliferation of tumor cells by binding to HER2, thereby blocking ligand-independent receptor dimerization and subsequent downstream signaling that leads to irregular cellular proliferation. Trastuzumab also elicits antibody-dependent cellular cytotoxicity (ADCC) against tumor cells through concomitant binding to HER2 on tumor cells and Fcγ receptors on immune system effector cells. The mechanisms of action and indications for Kanjinti are the same as those for US-licensed Herceptin. Kanjinti has the same formulation, dosage form, strength, and route of administration as US-licensed Herceptin.

Analytical data submitted in the BLA support the conclusion that Kanjinti is highly similar to US-Herceptin. The applicant provided a comprehensive analytical similarity assessment comparing Kanjinti to US-Herceptin. Additionally, to justify the use of clinical data from patients treated with EU-Herceptin in the BLA, the applicant included data of three-way

comparisons amongst EU-Herceptin, US-Herceptin, and Kanjinti. The analytical data supports similar biological activities pertaining to both Fab and Fc portions of the molecule, primary structures including post-translational modifications, higher order structures, product-related species, degradation pathways, thermal stability, and drug product attributes. The extent of analytical characterization data provided is robust. Known and potential mechanisms of action of trastuzumab were evaluated by multiple orthogonal methods sensitive to detect potential differences in the molecules (See Table 1 in Section IIA below). The numbers of product lots used in the analytical assessments were adequate to capture lot-to-lot variability.

The manufacturing processes for Kanjinti drug substance is well controlled and consistently produce product that is pure and potent. The drug substance process is qualified for removal of impurities and inactivation or removal of adventitious agents. The overall control strategy for drug substance and drug product is comprehensive for control of raw materials, process performance, and product quality attributes. ADCC activity of Kanjinti is controlled (b) (4)

During the review cycle, the applicant agreed to implement an FcγRIIIa binding test to the drug substance release specification. This test provides additional assurance that ADCC activity is fully controlled in commercial Kanjinti lots. Pending resolution of the GMP issues found on inspection of the drug product manufacturing facility, the current proposed manufacturing control strategy is sufficient to ensure process consistency and product quality.

II. Summary of Quality Assessments:

A. Analytical Data Assessment

To demonstrate that Kanjinti is highly similar to US-Herceptin, and to support the use of clinical data generated using EU-Herceptin as the comparator in breast cancer patients, the applicant performed pair-wise analytical comparisons of all 3 products. Twenty-two lots of Kanjinti, 23 lots of US-Herceptin, and 33 lots of EU-Herceptin were used in the comparative analytical studies. For some attributes, analytical comparisons were amended during the review cycle at the Agency's request to include a total of 29 lots of US-Herceptin. US-Herceptin and EU-Herceptin lots used in the analysis were collected over a period of approximately 5 years.

For attributes primarily influenced by the drug substance manufacturing process, statistical analyses included only independent lots of Kanjinti drug product or drug substance. The applicant applied a tier-based system for evaluating similarity based on each attribute's potential to impact clinical outcomes. Potency and ADCC attributes reflect mechanisms of action and were therefore evaluated with the highest statistical rigor. The selection of methods and assignment of attributes to different tiers are justified. Data provided in the analytical assessment were collected using methods appropriately validated or qualified for intended use.

The following Table 1 summarizes the quality attributes and test methods utilized in the analytical assessment.

Table 1. Attributes and Methods used in Analytical Similarity Assessments

Quality Attributes	Methods
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Biological activity	• Potency by proliferation inhibition bioassay (BT-474 cells) • Potency by proliferation inhibition in NCI-N87 gastric cancer cells • Lack of proliferation inhibition in non-amplified HER2 MCF7 cells • Synergy with chemotherapeutic by proliferation inhibition (NCI-N87 cells) • HER2 binding by ELISA • HER2 binding by SPR • HER2 signaling by inhibition of AKT phosphorylation activity • FcRn binding by AlphaScreen • FcγRIIIa (158V) binding by AlphaLisa • FcγRIIIa (158F) binding by AlphaLisa • ADCC activity by PBMC effector cells • ADCC activity by NK92 effector cells • Lack of ADCC in HER2 negative cells by NK92 effector cells • ADCP activity by PBMC effector cells • FcγRIIa (131H) binding by AlphaLisa • FcγRIa binding by SPR • FcγRIIb binding by SPR • FcγR binding on primary macrophages by flow cytometry • FcγRIIIb binding by SPR • C1q binding by ELISA • Lack of CDC activity in HCC2218 cells
Primary structure	• Intact molecular mass by ESI-TOF-MS • Reduced/deglycosylated molecular mass of HC and LC by ESI-TOF-MS • Reduced peptide map ○ Amino acid sequence ○ Deamidation, oxidation, and isomerization ○ Profile • Non-reduced peptide map ○ Disulfide structure ○ Profile • Glycan map by HILIC HPLC ○ Percent afucosylation ○ Percent high mannose ○ Percent galactosylation ○ Percent afucosylated galactosylation ○ Percent sialylation ○ Glycan map profile • Isoelectric point and profile by capillary isoelectric focusing • Amino acid analysis by extinction coefficient • Identity by ELISA
Higher order structure	• Fourier transform infrared spectroscopy • Near UV circular dichroism • Differential scanning calorimetry
Particles and aggregates	• Subvisible particles by MFI • Subvisible particles by HIAC • Submicron particles by field flow fractionation • Submicron particles by dynamic light scattering • Sedimentation velocity-analytical ultracentrifugation (AUC-SV)

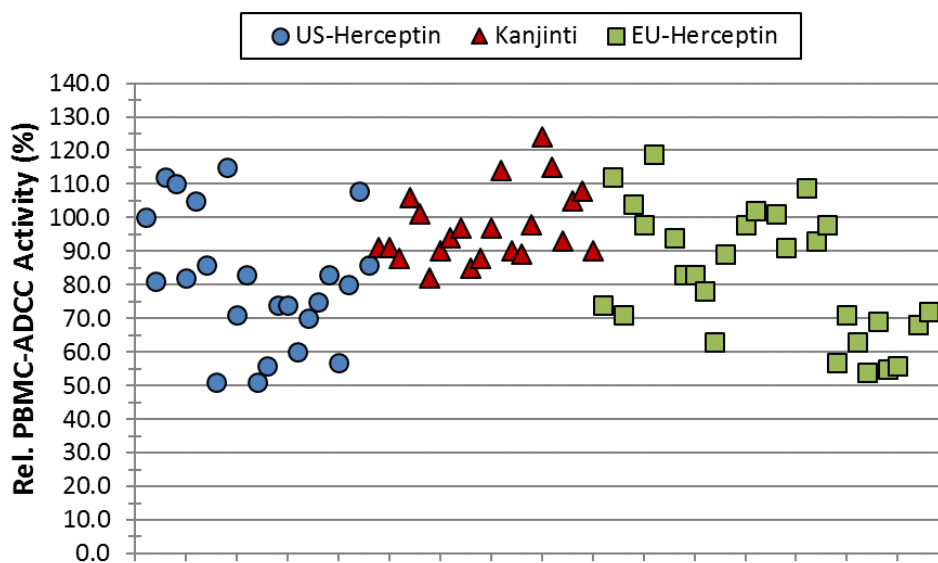
	• SE-HPLC with light scattering detection
Product-related substances and impurities	• SE-UHPLC • Reduced CE-SDS (rCE-SDS) • Non-reduced CE-SDS (nrCE-SDS) • Cation exchange-HPLC (CEX-HPLC)
Thermal stability and forced degradation	• 50°C forced degradation study (SE-UHPLC, rCE-SDS, nrCE-SDS, CEX-HPLC, Potency)
General properties	• Protein content • Reconstituted protein concentration • Reconstitution time
Process-related impurities	• HCP by ELISA • HCP by 2D-DIGE • HCP by LC/MS • Protein A ELISA • DNA by qPCR

The data demonstrate that Kanjinti, US-Herceptin, and EU-Herceptin have the same amino acid sequences apart from differences at the heavy chain C-terminal lysine residue. Differences in the levels of C-terminal lysine residue are justified based on current understanding that C-terminal lysine residues of monoclonal antibodies are cleaved in the bloodstream shortly after intravenous administration. The data also demonstrate similar higher order structures, which is supported by both biochemical and functional testing results.

Similar potency between Kanjinti, US-Herceptin, and EU-Herceptin was demonstrated in a bioassay that measures dose-dependent inhibition of proliferation in BT-474 cells derived from breast cancer. Comparisons for all three products met pre-defined statistical equivalence criteria. Similar bioactivity between the 3 products was confirmed in an orthogonal assay that measures anti-proliferation activity against NCI-N87 cells derived from gastric cancer. Results from multiple orthogonal HER2 binding assays support Kanjinti, US-Herceptin, and EU-Herceptin have similar affinities for the targeted HER2.

Similar ADCC activity between Kanjinti, US-Herceptin, and EU-Herceptin was demonstrated when using peripheral blood mononuclear cells (PBMC) as immune system effector cells. The PBMCs were isolated from healthy donors heterozygous for FcγRIIIa (158V/F) alleles. Comparisons for all three products met pre-defined statistical equivalence criteria. ADCC results for Kanjinti, US-Herceptin, and EU-Herceptin using the PBMC method are provided in Figure 1 below.

Figure 1. PBMC-ADCC Activity for Kanjinti, US-Herceptin, and EU-Herceptin

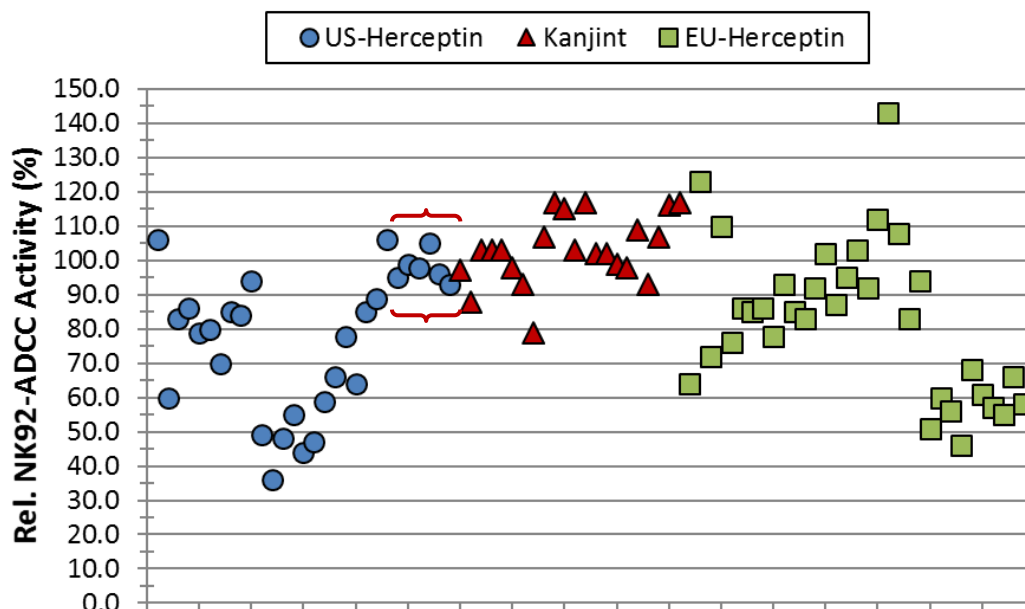


Source: FDA analysis of data from the 351(k) BLA submission

All tests described in Table 1 above met pre-defined statistical or qualitative criteria for assessing high similarity of Kanjinti to US-Herceptin and establishing the analytical component of the three-way scientific bridge between Kanjinti, US-Herceptin, and EU-Herceptin with some exceptions discussed in this section below. In instances where differences were observed, residual uncertainty was mitigated by additional information or data to support no meaningful impact on biological behavior of the molecule. These differences do not preclude a determination that Kanjinti is highly similar to US-Herceptin or the establishment of the analytical component of the three-way scientific bridge.

- Differences in ADCC activity between Kanjinti and US-licensed Herceptin were observed by an orthogonal method that uses a natural killer cell line (NK92) as effector cells. Unlike heterogenous PBMC effectors, NK92 cells are engineered to express high levels of the high affinity variant of FcγRIIIa (158V), which can influence assay sensitivity. The applicant asserted that equivalence was not met due to a temporal trend towards lower ADCC values observed in US-Herceptin. Data from 6 additional lots of US-Herceptin with more recent expiry dates were provided in support of this claim. NK92 ADCC values for the 6 additional reference product lots range from 93-105%, which are all higher than the mean NK92 ADCC value of 71.9% for lots provided in the original BLA. To illustrate this, Figure 2 below plots US-Herceptin and EU-Herceptin lots arranged by expiry date along the x-axis from earliest (left) to most recent (right) expiry dates against relative percent ADCC values on the y-axis. This Figure 2 shows amended NK92 ADCC results with red brackets added to mark the 6 additional US-Herceptin lots.

Figure 2. NK92-ADCC Activity for Kanjinti, US-Herceptin, and EU-Herceptin



Source: FDA analysis of data from the 351(k) BLA submission

Based on data from recent lots of US-Herceptin, FDA assessed that the difference between Kanjinti and US-Herceptin is potentially overestimated by the current NK92 ADCC dataset. The period of out-of-trend (low) results in the innovator product lots (US-Herceptin and EU-Herceptin) impacted the statistical equivalence testing. Findings of trends over a period of time in the innovator products are independently corroborated by published data.¹ The resulting residual uncertainty is mitigated by equivalent results from the PBMC-ADCC assay, which is acceptable to evaluate ADCC activity for trastuzumab. The PBMC-ADCC assay has been found acceptable to statistically evaluate ADCC activity for other trastuzumab biosimilar programs. Additionally, similarity was demonstrated for multiple quality attributes that are tightly linked to ADCC activity, including percent afucosylation and FcγRIIIa binding. The minor differences in NK92 ADCC activity do not preclude a demonstration that Kanjinti and US-Herceptin are highly similar.

- Differences in non-glycosylated heavy chain (NGHC) levels were observed between Kanjinti and US-Herceptin. NGHC can impact binding to Fc receptors and subsequent Fc effector functions. Percent NGHC levels are on average 0.5% lower in Kanjinti lots compared to US-Herceptin and EU-Herceptin. The overall levels of NGHC are very low (<1%) for all three products. The minor differences in NGHC did not impact demonstration of similarity for ADCC activity or FcγRIIIa binding results. Therefore, these differences do not preclude a demonstration that Kanjinti and US-Herceptin are highly similar.

¹ Kim, et.al. 2017. MABS. 9(4):704.

- Differences in partially reduced species measured as pre-peaks by nrCE-SDS were observed between Kanjinti and US-Herceptin. Partially reduced species reflect antibody with open disulfide structures, which can impact potency. Percent partially reduced species levels are on average 0.5% higher in Kanjinti lots compared to US-Herceptin and EU-Herceptin. However, the overall levels of partially reduced species are low (<2%) for all three products. The minor differences in partially reduced species did not impact demonstration of similarity for biological activity tests. Published data suggest partially reduced species convert back to fully disulfide linked antibodies under physiological conditions.² Therefore, these differences do not preclude a demonstration that Kanjinti and US-Herceptin are highly similar.
- Differences in charge variants measured by cation exchange high performance liquid chromatography (CEX-HPLC) were observed between Kanjinti and US-Herceptin. CEX-HPLC resolves charge variants into groups of acidic peaks, basic peaks, and the main peak. The levels of acidic peaks in Kanjinti are higher compared to US-Herceptin and EU-Herceptin, with differences on average of <10%. Levels of basic variants are within the quality range of US-Herceptin. When comparing first timepoints, slightly lower levels of basic variants were observed in Kanjinti compared to US-Herceptin and EU-Herceptin. However, because basic variant levels increase during storage, this difference is expected due to ages of the lots at the time of testing.

Acidic peaks contain species of deamidation at LC (Asn30) and HC (Asn55), non-consensus glycosylation, glycation, and fragments. The applicant characterized acidic charge variants in all three products by additional fractionation and extended testing. The fractions contain the same types of variants across all three products. Additional analyses found the differences in acidic variants are primarily driven by differences in non-consensus glycosylation and partially reduced species. Biological characterization data from highly enriched acidic fractions support low impact to bioactivity, including potency and ADCC activity. The differences in acidic variants did not impact demonstration of similarity for biological activity tests. Therefore, these differences do not preclude a demonstration that Kanjinti and US-Herceptin are highly similar.

- Differences in C1q binding were observed between Kanjinti and US-Herceptin. The results met pre-defined acceptance criteria. It was observed, though, that Kanjinti shows higher average relative binding to C1q compared to US-Herceptin and EU-Herceptin. Binding to C1q can impact complement dependent cytotoxicity (CDC). Regulatory proteins expressed on the surface of some tumor cells can mitigate CDC activity. Consistent with this observation, although trastuzumab binds C1q, CDC activity does not appear to contribute significantly to the mechanism of action. The lack of trastuzumab-mediated CDC activity is demonstrated by an *in vitro* bioassay using HER2-overexpressing HCC2218 breast cancer cells. The difference in C1q binding did not impact CDC activity results. Therefore, these minor differences do not preclude demonstration that Kanjinti and US-Herceptin are highly similar.
- Reconstituted protein concentration pair-wise comparison between Kanjinti and US-Herceptin did not meet pre-defined quality range criteria. Four out of 29 lots of Kanjinti fell below the US-Herceptin quality range. The reconstituted protein concentrations for these 4 lots are within 0.3

² Wang, et.al. 2014. J.Pharm.Biomed.Anal. 102(5):519.

mg/mL of the US-Herceptin range and within 5% of the target concentration of 21 mg/mL. The difference is within the variability of reconstitution. Protein concentration variability is influenced by the drug product manufacturing control strategy. The commercial drug product manufacturing controls were later optimized. Process validation data support commercial lots produced by the current process fall well within the quality range. Therefore, these differences do not preclude a demonstration that Kanjinti and US-Herceptin are highly similar.

In summary, the analytical data support the conclusion that Kanjinti is highly similar to US-Herceptin. EU-approved Herceptin was used as a comparator in clinical studies provided in support of this BLA. Analytical comparisons of US-Herceptin, Kanjinti, and EU-Herceptin provided in the BLA support establishment of the analytical component of the three-way scientific bridge. The immunogenicity assays used to evaluate anti-drug antibodies in comparative immunogenicity studies provided in support of this BLA are adequately validated.

B. CQA Identification, Risk and Lifecycle Knowledge Management

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

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

CQA	Risk	Origin	Control Strategy	Other
Inhibition of Proliferation (potency)	Efficacy	Intrinsic to the molecule. Impacted by isomerization (HC Asp¹⁰²), aggregation, fragments, and deamidation. Decreases upon exposure to heat and light. Minimal change is expected when stored under recommended storage conditions.	(b) (4)	Cell based bioassay method is stability indicating.
HER2 binding (potency)	Efficacy	Intrinsic to the molecule. Impacted by fragments. Decreases upon exposure to heat.		N/A

		Minimal change is expected when stored under recommended storage conditions.		
Effector function/ADCC (potency)	Efficacy	Intrinsic to the molecule. Impacted by levels of core fucose and galactosylation. Decrease upon exposure to heat consistent with decrease in HER2 binding. Minimal change is expected when stored under recommended storage conditions.	(b) (4)	No CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A
Isomerization at Asp102 in the HC CDR (product-related impurity)	Efficacy (isomerization may reduce potency or effector function) and Immunogenicity	Production culture. May increase during storage of DP. Increases upon exposure to heat and low pH.		CEX-HPLC method is stability indicating.
Dimer/High Molecular Weight (HMW) Species/Aggregates (Product-related impurities)	Efficacy and Immunogenicity	Production culture and potential minor impact from DP process. May increase during storage of DP. Increase upon exposure to heat and light.		SE-UHPLC method is stability-indicating
Fragments (Product-related impurity)	Immunogenicity and Efficacy	Cell culture process Increase upon exposure to heat. No change through expiry when stored		N/A

		under recommended conditions.		
Glycosylation— afucosylation (Product related variant)	Efficacy (Effector function)	Cell culture process	(b) (4)	N/A
Glycosylation— high mannose (Product related variant)	Efficacy (Effector function) and Pharmacokinetics	Cell culture process		N/A
Glycosylation— galactosylation (Product related variant)	Efficacy (Effector function)	Cell culture process		N/A
Partially reduced species (Product-related impurity)	Efficacy	Production culture and harvest processes Increases upon exposure to heat. Minimal change is expected under recommended storage conditions.		N/A
Deamidation at Asn30 Asn55 (Product-related impurities)	Efficacy and Immunogenicity	Manufacturing process Increases upon exposure to heat. Minimal change is expected under recommended storage conditions.		CEX-HPLC method is stability-indicating.
Sequence variants at T259A and N84T (Product-related variants)	Immunogenicity	Production cell line		N/A
pH (General)	Safety and Efficacy	Formulation		N/A

Protein concentration (General)	Efficacy	Manufacturing process	(b) (4)	N/A
Osmolality (General)	Safety	Formulation		N/A
Polysorbate concentration (General)	Safety	Formulation		N/A

C. Drug Substance trastuzumab-anns Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

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

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (general)	Safety	Manufacturing process	(b) (4)	N/A
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (process-related impurity)	Low hypothetical safety or immunogenicity risk	Production cell line		N/A

Protein A (process-related impurity)	Immunogenicity	Leaching of protein A (b) (4) [REDACTED] [REDACTED] [REDACTED]	(b) (4)	N/A
(b) (4) (Process-related impurity)	Safety	Process-related impurity used (b) (4) [REDACTED]		N/A
(b) (4) (Process-related impurity)	Safety	Process-related impurity used (b) (4) [REDACTED]		N/A
(b) (4) (Process-related impurity)	Safety	Process-related impurity used in the production bioreactor		N/A
(b) (4) (Process-related impurity)	Safety	Process-related impurity used in the production bioreactor		N/A
(b) (4) (Process-related impurity)	Safety	Process-related impurity used in the production bioreactor		N/A

			(b) (4)	
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
(b) (4)	Safety	Process-related impurity used in the production bioreactor		N/A
(Process-related impurity)				
Viruses (Contaminant)	Safety	Contamination during manufacture		N/A
Mycoplasma (Contaminant)	Safety	Contamination during cell culture operations		N/A
Leachables (Process-related impurity)	Safety	Manufacturing components and DS container closure system (CCS)		N/A
Bacterial endotoxins (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process		N/A
Bioburden	Safety, purity, and efficacy	Bioburden can be introduced by raw		N/A

(Contaminant)	(degradation or modification of the product by contaminating microorganisms)	materials and throughout the manufacturing process	(b) (4)
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- **Description:**

Trastuzumab-anns is a recombinant humanized IgG1κ monoclonal antibody produced in CHO cells that targets human epidermal growth factor receptor 2 (HER2). The antibody consists of two heavy chains (449 amino acids each) and two light chains (214 amino acids each). Each heavy chain contains an N-linked glycan site at asparagine 300 (Asn300) with greater than 99.8% occupancy. The predominant glycan species are asialylated core fucosylated biantennary with varying degrees of terminal galactose. Trastuzumab-anns has an average molecular weight of 148,222 Da and an isoelectric point of 8.8 (main species). The theoretical and experimental extinction coefficient is 1.5 cm⁻¹ (mg/mL)⁻¹ at A₂₈₀ nm.

- **Mechanism of Action (MoA):**

Multiple mechanisms of action are proposed for trastuzumab-anns, which binds to the extracellular domain subdomain IV of HER2. Overexpression of HER2 on cancer cells results in persistent and ligand-independent activation of downstream signaling, which in turn leads to aberrant cell proliferation. Trastuzumab-anns binding to HER2 blocks this ligand-independent signaling in cancer cells, thereby inhibiting cellular proliferation. A second proposed mechanism of action is activation of antibody-dependent cellular cytotoxicity (ADCC) through concomitant binding of trastuzumab-anns to HER2 on cancer cells and Fcγ receptors on immune effector cells. Trastuzumab-anns also binds to complement component 1q (C1q) of the classical complement pathway. However, complement-dependent cytotoxicity (CDC) is not detected for trastuzumab-anns and therefore not considered a major mechanism of action.

- **Potency Assay:**

Inhibition of proliferation is tested by a quantitative cell-based assay using BT-474 human breast tumor cells that overexpress HER2. Cell proliferation is measured using a luminescent assay reagent that detects ATP. The measured luminescent signal is proportional to the amount of ATP, which is proportional to the number of cells present. Trastuzumab-anns inhibits BT-474 cell proliferation resulting in a dose-dependent loss of luminescent signal. Relative potency values are calculated using model curve fits from four-parameter logistic curves of dose response data. Potency is reported as a percentage relative to the reference standard. The cell-based bioassay is appropriately validated.

Asparagine-linked (N-linked) oligosaccharides are assessed by hydrophilic interaction chromatography (HILIC) glycan mapping as surrogate for ADCC activity. The N-linked glycan are enzymatically released using N-glycosidase F (PNGase F) and the terminal N-acetylglucosamine (GlcNAc) is derivatized with a fluorophore. The labeled glycan are then separated using a hydrophilic interaction column and evaluated by a fluorescence detector. (b) (4)

(b) (4)

Additional

information is located in the Product Quality technical review.

- **Reference Materials:**

A two-tier reference standard qualification program is in place consistent with ICH Q6B recommendations. The current primary and working reference standards are stored at -

(b) (4)

- **Critical starting materials or intermediates:**

A two-tiered cell banking system consisting of a master cell bank (MCB) and working cell bank (WCB) is in place to ensure continued source of product. The production cell

(b) (4)

- **Manufacturing process summary:**

The DS manufacturing process starts with

(b) (4)

(b) (4)

The BLA contains sufficient information and validation results that indicate the raw material program, facilities and equipment, manufacturing process, release, and stability programs are adequately controlled resulting in the production of a consistent product. Additional information is in the Product Quality and DS Microbiology primary technical reviews.

- **Container closure:**

(b) (4)

- **Dating period and storage conditions:**

The data provided in the BLA support the establishment of a shelf life of (b) (4) months for trastuzumab-anns drug substance when stored at (b) (4)

D. Drug Product [Kanjinti] 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.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout DP manufacturing process	(b) (4)	N/A

Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contamination may be introduced throughout DP manufacturing process and raw materials	(b) (4)	N/A
Container Closure Integrity (Sterility assurance)	Safety (breach in the container closure system may impact product sterility)	May be impacted by storage conditions		N/A
Color and clarity of solution (General)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Appearance of reconstituted solution—visible particles (product or process-related impurities)	Safety and Immunogenicity	Manufacturing process, formulation, interaction with container closure system		N/A
Appearance—lyophilized cake	Safety and Efficacy	Manufacturing process		N/A
Moisture content	Safety and Efficacy	Manufacturing process		N/A
Reconstitution time	Safety and Efficacy	Manufacturing process, formulation		N/A
Subvisible particles	Safety and Immunogenicity	Manufacturing process and storage		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		N/A

- **Potency and Strength:**

Kanjinti is supplied at 420 mg/vial. Potency is defined as the percent activity relative to reference material. The cell-based potency assay is the same as described in the DS

section of this memo. The DP specification for potency is (b) (4) for release and stability.

- **Summary of Product Design:**

Kanjinti is supplied in a 50 mL glass vial as a sterile, multi-dose, preservative-free lyophilized powder for reconstitution. The reconstituted product is intended for dilution in saline for IV infusion. Kanjinti is formulated in 4.2 mM L-histidine, 51 mM α,α -trehalose, 0.008% (w/v) polysorbate 20 at pH 6 (b) (4). Reconstitution with 20 mL diluent yields a solution containing 21 mg/mL trastuzumab-anns at a pH of 6 (b) (4). The deliverable amount is 420 mg. (b) (4)

(b) (4) Kanjinti is intended for reconstitution with 20 mL bWFI for multi-dose or 20 mL of sterile WFI (sWFI) for single use. When reconstituted with bWFI, Kanjinti is stored for up to 28 days at 2-8°C.

- **List of Excipients:**

Excipients include L-Histidine (USP, PhEur, JP), L-Histidine hydrochloride monohydrate (PhEur, JP), α,α -trehalose dihydrate (USP/NF, PhEur, JP), and polysorbate 20 (USP/NF, PhEur, JPE).

- **Reference Materials:**

The same reference material is used for testing DS and DP.

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**

The primary container closure system for Kanjinti consists of a 50 mL (b) (4) glass vial that is closed with a 20 mm (b) (4) stopper and sealed with a 20 mm flip-off aluminum seal with plastic button. The secondary packaging consists of a carton constructed of solid paperboard to shield the product from light.

(b) (4)

- **Dating period and storage conditions:**

The stability data in the BLA support a shelf life for Kanjinti of 36 months when stored at the recommended storage condition of 2-8°C. (b) (4)

(b) (4). Stability data in the BLA support storage of the reconstituted product for 28 days at 2-8°C protected from light.

E. Novel Approaches/Precedents:

None

F. Any Special Product Quality Labeling Recommendations:

Store Kanjinti refrigerated at 2-8°C and protected from light. Do not shake. Do not freeze the reconstituted solution.

G. Establishment

Overall Facility Recommendation:				
Drug Substance				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
(b) (4)			Drug substance manufacture	Acceptable.
			Drug substance in-process and lot release testing	
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320	2026154	Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank storage Manufacture of working cell banks	Acceptable
Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road Dun Laoghaire,	3002808497	Drug substance in-process, lot release	Acceptable

	Co. Dublin, Ireland		and stability testing, and storage	
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817	3003359885	Unprocessed bulk mycoplasma testing Drug substance in-process, lot release and stability testing	Acceptable
Amgen Manufacturing Limited (AML)	State Road 31, Km 24.6, Juncos, Puerto Rico 00777-4060	1000110364	Drug substance in-process, lot release, and stability testing	Acceptable
(b) (4)			Unprocessed bulk mycoplasma and adventitious virus testing	Acceptable
			Unprocessed bulk mycoplasma and adventitious viral testing	Acceptable

Drug Product				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
(b) (4)			Drug product manufacture	Withhold
			Drug product in-process and lot release testing. Diluent manufacture (b) (4)	
Amgen Inc. Thousand Oaks Facility (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320	2026154	Drug product lot release and stability testing. (b) (4)	Acceptable

Amgen Technology Ireland Unlimited Company (ADL)	Pottery Road Dun Laoghaire, Co. Dublin, Ireland	3002808497	Drug product lot release and stability testing. (b) (4)	Acceptable
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way, West Greenwich, Rhode Island, 02817	3003359885	Drug product lot release and stability testing	Acceptable
Amgen Manufacturing Limited (AML)	State Road 31, Km 24.6, Juncos, Puerto Rico 00777-4060	1000110364	Packaging and labeling Drug product lot release and stability testing	Acceptable

H. Facilities:

A pre-licensure inspection (PLI) was conducted from (b) (4) at the (b) (4) drug substance manufacturing facility. A ten-item Form FDA 483 was issued to the Firm covering (b) (4)

The CDER inspectors recommended VAI. OPF/DIA conducted a review of the Form FDA 483 observations, EIR and exhibits, and the firm's written responses to the Form FDA 483. Based on the completed inspectional assessment by OPF/DIA, the Patheon Biologics, B.V. drug substance manufacturing facility is recommended for approval.

A PLI was conducted from (b) (4) at the (b) (4) drug product manufacturing facility. A nine-item Form FDA 483 was issued at the end of inspection for (b) (4)

The inspector made an initial Withhold recommendation for the application. The submission is recommended for withhold from a facilities perspective. Satisfactory resolution of these deficiencies is required before this BLA can be approved. Based on this inspectional assessment by OPF/DIA, the (b) (4) drug product manufacturing facility is not recommended for approval. Additional information is located in the Facilities Assessment technical document.

The Form FDA 483 issued at the end of inspection of the (b) (4) facility included the following observation: (b) (4)

On May 11th, FDA sent an email request to Amgen for a telecon to verify that only (b) (4) are intended for use in commercial manufacturing. In response to this request, Amgen provided the following statement by email:

We confirm that only (b) (4) are going to be used for commercial manufacturing. We propose to update Sections 3.2.P.3.3 and 3.2.A.1 to remove references to (b) (4) and will officially submit the updated sections to the BLA early next week.

On May 14th, Amgen submitted an amendment to the BLA confirming that only (b) (4) are going to be used for commercial manufacturing. The amendment also updates sections 3.2.P.3.3—Description of Manufacturing Process and Process Controls, 3.2.P.3.5—Process Validation [440 mg, (b) (4)], and 3.2.A.1—Facilities and Equipment (b) (4) to remove references to (b) (4). The information provided in the amendment is adequate to support the conclusion that (b) (4) operations for Kanjinti will be performed using only those (b) (4) in the license that are supported by sterility assurance and performance qualification results.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. Annual stability protocol for drug substance
2. Stability protocol for extension of drug substance shelf life
3. Protocol for qualification of future working cell banks
4. Protocol for qualification of future primary and working reference standards

(b) (4)

ii. Outstanding issues/residual risk:

See Additional Comments in section IC above

iii. Future inspection points to consider: PLI inspection will be considered based on CR re-submission.

b. Drug Product

i. Protocols approved:

1. Annual stability protocol for drug product

2. Stability protocol for extension of drug product shelf life
 3. Stability protocol (b) (4)
 4. Comparability protocol for addition of Production Module 2 at Amgen Technology Ireland UC, Dun Laoghaire, Ireland as an alternate manufacturing facility for drug product.
- ii. Outstanding issues/residual risk:
See CR issues in section IB and Additional Comments in section IC above
- iii. Future inspection points to consider: PLI inspection will be considered based on CR re-submission.

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 source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity		X	
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)	X		
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]		X	
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	X	
23.		Process	X	
24.		Analytical Methods	X	
25.		Other	X	
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)	X		
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients	X	
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin	X	
35.		Novel	X	
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release			
40.	Other {fill-in}		X	



Patrick
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Howard
Anderson

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING QAL: Reyes Candau-Chacon, Ph.D.

BLA:	761073
Applicant:	Amgen, Inc.
US License Number:	1080
Submission Reviewed:	351(k) BLA
Product:	ABP 980, proposed biosimilar to US approved trastuzumab
Indication:	Adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer
Dosage Form:	Lyophilized powder for intravenous infusion, 420 mg
Manufacturing Sites:	Drug product: (b) (4) (b) (4)
FDA Receipt Date:	28 July 2017
Action Date:	28 May 2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective. Due to the outcome of the drug product manufacturing facility, a Complete Response Letter is being issued to the applicant.

The following additional comments should be communicated to the applicant:

1. (b) (4) were not included for (b) (4). Provide (b) (4) sterilization validation information for the (b) (4) in section 3.2.P.3.5 of the BLA.

2. Media fill simulations to support the ABP 980 (b) (4) did not include (b) (4). Perform media fill simulations that include (b) (4).
(b) (4)
(b) (4)
3. The (b) (4) validation data provided in the BLA did not include (b) (4).
(b) (4)
(b) (4)
(b) (4)
4. The ABP 980 manufacturing process does not include (b) (4). Implement the necessary equipment modifications to designate (b) (4).
(b) (4)

Conclusion

- I. The drug product part of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. Refer to Panorama for CGMP status of manufacturing and testing facilities.



Jessica
Hankins

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Reyes
Candau-Chacon

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: 05/22/2018
To: Administrative File, STN 761073/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao (Peter) Qiu, Ph.D., Supervisory Consumer Safety Officer
CDER/OPQ/OPF/DIA, Branch 1 Chief
Subject: New Biologic License Application (BLA)
US License: 1080
Applicant: Amgen Inc.
Mfg Facility: Drug Substance: (b) (4) for ABP 980 DS
Drug Product: (b) (4)
Product: KANJINTI (trastuzumab-atzu)
Dosage: Lyophilized powder, 420 mg, Intravenous infusion
Indication: For adjuvant breast cancer, metastatic breast cancer, and metastatic gastric cancer.
Due Date: May 28, 2018

RECOMMENDATION: This submission is recommended for withhold from a facilities assessment perspective. During a recent inspection of the (b) (4) manufacturing facility for this BLA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this BLA can be approved.

SUMMARY

The subject BLA proposes manufacture of ABP 980 DS at (b) (4) and DP at the (b) (4). Both locations are multi-product manufacturing facilities. The final dosage form for the 420 mg presentation consists of a 50 cc (b) (4) glass vial, with 20 mm (b) (4) stopper, and aluminum flip off dust cover. (b) (4) The container closure system is a 20 CC (b) (4) glass vial, with a 20 mm (b) (4) stopper, and aluminum seal with flip-off dust cover.

ABP 980 has been developed as a biosimilar product to the reference product Herceptin (trastuzumab [US]) (BLA 103792, license is held by Genentech, Inc., a member of the Roche

Group). ABP 980 and the reference product are recombinant humanized immunoglobulins isotype class G subclass 1 (IgG1) kappa monoclonal antibodies expressed in Chinese hamster ovary cells. Like the reference product, ABP 980 binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein. ABP 980 and the reference product have the same mechanism of action, inhibiting the ligand independent HER2 signaling pathway.

The facilities supporting ABP 980 DS manufacture, testing and storage are provided under Table 1, with facilities supporting ABP 980 DP manufacture, testing and storage included under Table 3.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

The proposed ABP 980 DS Manufacturer, Testing and Storage Facilities are provided in Table 1.

TABLE 1: Manufacturers for ABP 980 DS

Site Name	Address	FEI #	Responsibility
Amgen, Inc. (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320	2026154	DS in-process, lot release, and stability testing, along with MCB and WCB storage, and manufacture of WCBs.
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777	1000110364	DS in-process, lot release, and stability testing.
Amgen Technology Ireland UC (ADL)	Pottery Road Dun Laoghaire Ireland	3002808497	DS in-process, lot release and stability testing, and storage.
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way West Greenwich, RI 02817	3003359885	DS unprocessed bulk mycoplasma testing, and DS in-process, and lot release and stability testing.
(b) (4)			DS unprocessed bulk mycoplasma and adventitious viral testing.
			DS unprocessed bulk mycoplasma and adventitious viral testing.
			DS manufacture and in-process and lot release testing.

Reviewer Comment 1: *The facilities used for Manufacture, Testing and Storage of ABP 980 DS were adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

- Amgen, Inc. (FEI: 2026154) - WCB and MCB Manufacture, Storage and DS Testing

- Inspection Conducted 08/14 - 21/2017 by PHRM4: This was a PAI of a combination product (drug and device constituents) manufacturer, clinical manufacturer, distribution center, testing lab, and corporate headquarters. The profile codes DKA and IDD were covered. No Form FDA was issued, with a single verbal observation discussed with the firm. The inspection was classified NAI. The prior two GMP inspections conducted 05/16/2017 and 04/19/2017 were VAI and NAI, respectively, with the inspectional history for the firm including Quality, Facilities and Equipment, Production, Materials and Laboratory Control Systems.

- Amgen Manufacturing Ltd AML (FEI: 1000110364) - DS Testing

- Inspection Conducted 07/12 - 17/2017 by MDRHC: This was a comprehensive inspection of a biologics (biotech) API/DS, sterile DP, combination products, and oral-solid-dosage manufacturer. The inspection included coverage for CAPAs, Management Controls, Design Controls and Production and Process Controls subsystems. No Form FDA was issued, with the inspection classified NAI. The prior two GMP inspections conducted 05/10/2017 and 01/22/2016 were VAI, with the inspectional history for the firm including Quality, Facilities and Equipment, Production (includes packaging and labeling), Materials, and Laboratory Systems.

- Amgen Technology Ireland UC ADL (FEI: 3002808497) – DS Testing and Storage

- Inspection Conducted 09/14 - 22/2017 by IOG-MPT: This was a GMP inspection of a biotech sterile drug manufacturer. Quality, Production, Equipment and Facilities and Laboratory Systems were covered, with partial coverage of the Materials System. A 2-Item Form FDA 483 was issued, with verbal observations discussed with the firm. The inspection was classified VAI. The prior two GMP inspections conducted 12/08/2015 and 04/02/2015 were NAI and VAI, respectively.

- Immunex Rhode Island Corporation (FEI: 3003359885) - DS Testing

- Inspection Conducted 07/10 - 17/2017 by PHRM1: This was a GMP inspection of a manufacturer of therapeutic bulk DS intended to be used in sterile injectable drug products. Quality, Production, Facilities and Equipment, and Laboratory Control Systems were covered. No Form FDA 483 was issued, with the inspection classified NAI. The prior two GMP inspections conducted 02/03/2017 and 04/22/2016 were VAI.

-

(b) (4)

- **Current Prior Approval Inspection Decision**

- o Amgen, Inc. (FEI: 2026154) - WCB and MCB Manufacture, Storage and DS and DP Testing
 - Approve facility based on profile
- o Amgen Manufacturing Ltd AML (FEI: 1000110364) - DS and DP Testing and DP and Diluent Packaging and Labeling
 - Approve facility based on profile
- o Amgen Technology Ireland UC ADL (FEI: 3002808497) - DS, DP and Diluent Testing
 - Approve facility based on profile
- o Immunex Rhode Island Corporation (FEI: 3003359885) - DS and DP Testing
 - Approve facility based on profile

Reviewer Comment 2: *The proposed facilities for manufacture and testing of ABP 980 DS are currently in a state of compliance and are acceptable from a facilities assessment standpoint.*

3.2.A.1. DS SITE FACILITIES AND EQUIPMENT

- 3.2.A.1. Overview of ABP 980 manufacturing operations conducted at [REDACTED] (b) (4)

(b) (4)

➤ **3.2.A.1. Environmental Monitoring**

(b) (4)

➤ **3.2.P.3. DRUG PRODUCT FACILITIES**

ABP 980 DP: The primary container closure system for the ABP 980 420 mg presentation consists of a 50 cc (b) (4) glass vial, with a 20mm (b) (4) (b) (4), and an aluminum seal with flip-off dust cover.

(b) (4)

ASSESSMENT

The proposed ABP 980 DP (b) (4) manufacture, testing, storage and release facilities are listed in Table 3.

TABLE 3: Manufacturers for proposed ABP 980 DP (b) (4)

Site Name	Address	FEI #	Responsibility
(b) (4)			DP manufacture, in-process and lot release testing. (b) (4)
Amgen, Inc. (Referred to as Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320	2026154	DP lot release and stability testing (b) (4)
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777	1000110364	DP labeling and packaging, and lot release and stability testing. (b) (4)
Amgen Technology Ireland UC (ADL)	Pottery Road Dun Laoghaire Ireland	3002808497	DP lot release and stability testing (b) (4)
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI)	40 Technology Way West Greenwich, RI 02817	3003359885	DP lot release and stability testing.

Reviewer Comment 11: The facility used for manufacture, testing and storage of ABP 980 DP (b) (4) was adequately described and verified during the PLI conducted 04/26/2018 to 05/04/2018.

• **Prior Inspection History for DP Manufacturing, Testing, Storage and Release Sites**

0 (b) (4)

- o Amgen, Inc. (FEI: 2026154) - DP Testing
 - See Section 3.2.S.2., Drug Substance Facilities

- o Amgen Manufacturing Ltd AML (FEI: 1000110364) - DP Testing and DP Packaging and Labeling (b) (4)
 - See Section 3.2.S.2., Drug Substance Facilities

- o Amgen Technology Ireland UC ADL (FEI: 3002808497) - DP (b) (4) Testing
 - See Section 3.2.S.2., Drug Substance Facilities
- o Amgen Technology Ireland UC ADL (FEI: 3002808497) - DP (b) (4) Testing
 - See Section 3.2.S.2., Drug Substance Facilities
- o Immunex Rhode Island Corporation (FEI: 3003359885) - DP Testing
 - See Section 3.2.S.2., Drug Substance Facilities

- **Current Prior Approval Inspection Decision**

o (b) (4)

- o Amgen, Inc. (FEI: 2026154) - DP Testing
 - See Section 3.2.S.2., Drug Substance Facilities
- o Amgen Manufacturing Ltd AML (FEI: 1000110364) - DP Testing and DP (b) (4) Packaging and Labeling
 - See Section 3.2.S.2., Drug Substance Facilities
- o Amgen Technology Ireland UC ADL (FEI: 3002808497) - DP (b) (4) Testing
 - See Section 3.2.S.2., Drug Substance Facilities
- o Amgen Technology Ireland UC ADL (FEI: 3002808497) - DP (b) (4) Testing
 - See Section 3.2.S.2., Drug Substance Facilities
- o Immunex Rhode Island Corporation (FEI: 3003359885) - DP Testing
 - See Section 3.2.S.2., Drug Substance Facilities

Reviewer Comment 12: *The proposed facilities for manufacture and testing for ABP 980 DP (b) (4) are currently in a state of compliance and are acceptable from a facilities assessment standpoint.*

3.2.A.1. DP SITE FACILITIES AND EQUIPMENT

- 3.2.A.1. Overview of ABP 980 DP (b) (4) Manufacturing Operations Conducted at (b) (4)

(b) (4)

CONCLUSION

Adequate descriptions were provided for the facilities proposed for ABP 980 DS, DP (b) (4) manufacture; However, the subject BLA is recommended withhold from a facilities perspective as it pertains to the (b) (4) inspection conducted (b) (4)

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Wayne E.
Seifert -S

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

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING QAL: Reyes Candau-Chacon, Ph.D.

BLA:	761073
Applicant:	Amgen, Inc.
US License Number:	1080
Submission Reviewed:	351(k) BLA
Product:	Proposed biosimilar to US approved trastuzumab
Indication:	Adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer
Dosage Form:	Lyophilized powder for intravenous infusion, 420 mg
Manufacturing Sites:	Drug product: (b) (4) (b) (4)
FDA Receipt Date:	28 July 2017
Action Date:	28 May 2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective pending the inspection of the drug product manufacturing facility.

A total of four post-marketing commitments (PMCs) have been identified. PMCs 1 and 2 were noted in the review memo dated April 9, 2018 and are included below for completeness.

(b) (4)



(b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0033	04/11/2018	Response to Information Request
0034	04/13/2018	Response to Information Request
0035	04/17/2018	Response to Information Request

Reviewer comment: As noted in the interim review uploaded in Panorama on April 9, 2018, there are two 3.2.P. modules: (b) (4) ABP 980. The review of (b) (4) was completed in the interim review memo; however, additional information requests were pending for ABP 980 when the interim review memo was uploaded. The response to the information requests are reviewed in this addendum. The outstanding issues include the following items:

- Environmental monitoring action limits for the (b) (4) area.*
- (b) (4) sterilization validation information (b) (4)*
- Commitment to performing media fill simulations including (b) (4)*
- Addition of (b) (4).*
- Identification of environmental grade/class for drug product filtrations.*

Module 3.2 (ABP 980 – Lyophilized Power for Solution for Infusion)

P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

SATISFACTORY

Conclusion

- I. The drug product part of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective pending the inspection of the drug product manufacturing facility.
- II. Product quality aspects other than microbiology should be reviewed by OBP.

III. Inspection follow-up items were identified and communicated to DIA.

Microbiology Information Requests:

Sent: 4/12/18

1. The response to Question 2 of amendment 0033 indicates that the ABP 980 drug product is filled in a (b) (4) room. This is not consistent with current good manufacturing practice. The Agency recommends that high-risk drug products be filled using RABS or isolator technology. Implement the use of a RABS or isolator for the ABP 980 (b) (4)

Sent: 4/16/18

1. Implement the necessary equipment modifications (b) (4)
(b) (4)
Provide a timeline for the completion of the necessary equipment modifications and implementation of bioburden sampling prior to sterile filtration.



Jessica
Hankins

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING QAL: Reyes Candau-Chacon, Ph.D.

BLA:	761073
Applicant:	Amgen, Inc.
US License Number:	1080
Submission Reviewed:	351(k) BLA
Product:	Proposed biosimilar to trastuzumab (Kanjinti)
Indication:	Adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer
Dosage Form:	Lyophilized powder for intravenous infusion, 420 mg
Manufacturing Sites:	Drug product: (b) (4) (b) (4)
FDA Receipt Date:	28 July 2017
Action Date:	28 May 2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective pending the review of the following outstanding items:

- Environmental monitoring action limits for the (b) (4) area.
- (b) (4) sterilization validation information for the (b) (4).
- Commitment to performing media fill simulations including (b) (4).
- Addition of the (b) (4).
- Identification of environmental grade/class for drug product filtrations.

Two post-marketing commitments have been identified; however, additional PMCs are pending the review of the above information.

1.

(b) (4)

2.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	07/28/2017	Original BLA
0017	01/18/2018	Response to Information Request
0025	03/07/2018	Response to Information Request
0028	03/23/2018	Response to Information Request
0030	03/29/2018	Response to Information Request
0031	04/04/2018	Response to Information Request

Module 1 Regional

1.14 Labeling

The original submission stated that the drug product (DP) is reconstituted with sterile WFI, without preservative and if not used immediately, the reconstituted DP could be stored for (b) (4) at 2-8°C. Further the label indicated that the solution for infusion diluted in 0.9% saline should be stored at 2-8°C for (b) (4) prior to use. However, no microbial stability data was provided to support the label claim.

Reviewer comment: An information was sent to the applicant stated that microbial challenge data should be provided to support the label claim or that the label should be modified to indicate that the post reconstitution and post-dilution storage period be no more than 4 hours at 2-8°C. The applicant indicated in sequence 0017 that the label was revised to indicate that the DP reconstituted with sterile WFI be used immediately. Additionally, the applicant indicated in sequence 0025 that the label was revised to indicate that the DP solution diluted in 0.9% sodium chloride should be stored at 2-8°C for no more than 4 hours prior to use.

(b) (4)



Jessica
Hankins

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Reyes
Candau-Chacon

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 18 January 2018
To: Administrative File, **STN 761073/0**
From: Kathleen R. Jones, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV
Through: Reyes Candau-Chacon, Ph.D. Actg Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV
Subject: New 351 (k) Biologic License Application (BLA)
Applicant: Amgen Inc.
US License: 1080
Product: KANJINTI/ABP980
Dosage: 420 mg, lyophilized powder for intravenous infusion
Indication: For the treatment of adjuvant breast cancer, metastatic breast cancer, and metastatic gastric cancer.
Facilities:  (b) (4)

Receipt Date: 28 July 2017

Action date: 28 May 2018

Recommendation for Approvability: BLA 761073/0 is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Amgen Inc. has submitted 351(k) BLA 761073 to obtain approval of ABP 980. ABP 980 is a humanized monoclonal (IgG1) antibody against the human epidermal growth factor receptor 2 (HER2), and is a proposed biosimilar to Herceptin®. BLA 761073 was submitted in eCTD format on 28 July 2017. This review contains the assessment of the microbial quality attributes of ABP 980 bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Jessica Hankins.

Drug Substance Microbiology Information Reviewed

eCTD Sequence	Date	Description
0001	28 July 2017	Original BLA
0005	21 September 2017	IR Response; Modifications to 1.11
0008	24 October 2017	Modifications to 1.11
0009	30 October 2017	IR Response; Modifications to 1.11
0025	07 March 2018	Modifications to 3.2.S.2.1, 3.2.S.2.2, and 3.2.S.2.4

Full FDA Information Requests are provided at the end of this review memo.

Product Quality Microbiology Assessment: Drug Substance
MODULE 3.2.S DRUG SUBSTANCE

S.1 General Information

ABP 980 is a humanized monoclonal antibody against the HER2 receptor, and is produced in Chinese Hamster Ovary (CHO) cells. ABP 980 is proposed to bind to the extracellular domain of HER2, thereby inhibiting proliferation of HER2 overexpressed tumor cells in a dose-dependent manner.

The description is satisfactory

S.2 Manufacture

S.2.1 Manufacture(s)

The following facilities are used for the manufacture, release testing, and stability testing of ABP 980 drug substance. The information in the following table is from Tables 1 and 2 in section 3.2.S.2.1 in the submission.

Site	Responsibility
(b) (4)	Drug substance manufacture Drug substance in-process and lot release testing
Amgen Inc. (Amgen Thousand Oaks/ATO) One Amgen Center Drive, Thousand Oaks, CA USA FEI: 2026154	Drug substance in-process, lot release, and stability testing Master cell bank (MCB) and working cell bank (WCB) storage Manufacture of working cell banks
Amgen Technologies Ireland UC (Amgen Dun Laoghaire/ADL) Pottery Road Dun Laoghaire Ireland FEI: 3002808497	Drug substance in-process, lot release, stability testing, and storage
Immunex Rhode Island Corp. (Amgen Rhode Island/ARI)	Unprocessed bulk testing mycoplasma testing

40 Technology Way West Greenwich, RI 02817 USA FEI: 3003359885	Drug substance in-process, lot release, and stability testing
Amgen Manufacturing Limited (AML) Carr. 31 KM 24.6 Juncos, Puerto Rico 00777 USA FEI: 785800020	Drug substance in-process, lot release, and stability testing
* (b) (4)	Unprocessed bulk testing: mycoplasma and adventitious viral
* (b) (4)	Unprocessed bulk testing: mycoplasma and adventitious viral

*Contract Testing Laboratory

Reviewer's comment: The applicant originally included multiple testing sites for bioburden and endotoxin release testing. The applicant clarified in amendment 0025, dated 07 March 2018 that (b) (4) in-process and drug substance release testing is performed at (b) (4), and all other bioburden and endotoxin testing sites were removed from the submission.

Satisfactory

S.2.2 Overview of Manufacturing Process

(b) (4)



Kathleen
Jones

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Reyes
Candau-Chacon

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 7, 2018

TO: Julia Beaver, MD,
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Amendment to Establishment Inspection Report (EIR),
covering BLA 761073, ABP 980 (proposed biosimilar to
trastuzumab) sponsored by Amgen Inc., USA.

Inspection Summary

The current review is an amendment to the previous EIR review dated on **02/09/2018** because the inspected entity, Amgen Inc., provided an additional response to the Form 483 Observations.

In November 2017, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073 at Amgen, Thousand Oaks, CA.

During the inspection, significant objectionable conditions were observed that impacted the reliability of the audited studies, and Form FDA 483 was issued at the inspection close-out.

Amgen provided an additional response to the issues identified during the inspection. After evaluation of the firm's additional response, the OSIS scientist, Hasan A. Irier Ph.D., recommends to accept the data for Agency review.

Inspected Studies:

BLA 761073

Study Number: 20130119

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab(Herceptin®) in Healthy Male Subjects."

Dates of conduct: 06/14/2014 - 10/15/2014

Study Number: 20120283

Study Title: "A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer"

Dates of conduct: 04/29/2013 - 05/05/2016

Analytical site: Amgen Inc.,
720 Amgen Court, Thousand Oaks,
CA, 91320

I, Hasan A. Irier Ph.D. (OSIS), audited the analytical portion of the above studies at Amgen Inc., 720 Amgen Court, Thousand Oaks, CA, 91320 from **10/30/2017** to **11/3/2017**. At the end of the inspection, I observed objectionable conditions and issued Form FDA 483 (**Attachment 1**) to the analytical site. On November 21, 2017, Amgen Inc., provided a response to the Form 483 observations (**Attachment 2**). I evaluated the response, and requested Amgen to provide further clarification regarding their response provided specifically for Observation 2. On **February 21, 2018**, Amgen Inc., provided an additional response to Observation 2 (**Attachment 3**) to clarify the inclusion/exclusion of failed runs in the global assay precision assessment of the method for the anti-ABP980 antibody detection.

My evaluation of the firm's additional response specifically to the Observation 2 follows:

OBSERVATION 2: Global assay precision assessment did not include failed validation runs during Neutralizing antibody (NAb) assay validation MVR-000470 for ABP 980 and Herceptin-EU. Inclusion

of failed runs in the global assay precision resulted in assay precision not meeting the acceptance criteria.

Amgen's additional response to OSIS's Requests:

In the additional response (**Attachment 3**), Amgen provided further clarification on the classification of failed runs as "Technical Error" in the source documents provided during the inspection. In those runs, Drug Control (DC)/Positive Control (PC) values of "0.00" because of abnormally low assay signal values with the DC indicated a possible error in the preparation of the DC control.

OSIS's Evaluation:

Amgen's additional response appropriately addressed the discrepancies identified between the source documents presented during the inspection and the initial response to Form 483 Observation 2.

Conclusion:

After reviewing the inspectional findings, and evaluating the responses provided by Amgen, I conclude that the data from the audited studies are reliable. Therefore, I recommend that the data from the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073 at Amgen, Thousand Oaks, CA be accepted for further review.

Hasan A. Irier, Ph.D.
Pharmacologist

Final Classification:

VAI Amgen Inc.,
 Thousand Oaks, CA
 FEI#: 2026154

CC:
OTS/OSIS/Kassim/Choe/Haidar/Mitchell/Fenty-Stewart/Nkah/Johnson
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Irier
OND/OHOP/DOP1/Beaver/Tilley

Draft: HAI 2/22/18
Edit: YMC 2/28/18; JAK 3/6/18

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/Amgen Inc., Thousand Oaks, CA/S-BLA 761073_ABP 980 proposed biosimilar to trastuzumab

OSIS File #: BE 7590

FACTS: 11769182

ATTACHMENTS

Attachment 1. ABP980_Amgen_Form FDA 483-Signed

Attachment 2. 112082017_BLA 761073_Amgen 483 Response

Attachment 3. BLA 761073 KANJINTI - Additional Response to OSIS IR

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/s/

HASAN A IRIER

03/07/2018

Amended EIR Review, Amgen Inc., Thousand Oak, CA

JOHN A KADAVIL

03/07/2018

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 5, 2018

TO: Julia A. Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic/New Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Nucleus Network Limited,
Melbourne, Victoria, Australia

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study 20130119 (BLA 761073) conducted at Nucleus Network Limited, Melbourne, Victoria, Australia.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I found the data from the audited study 20130119 reliable. Thus, I recommend that the data from study 20130119 and other studies of similar design be accepted for further Agency review.

Inspected Study:

BLA 761073

Study Number: 20130119

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab (Herceptin®) in Healthy Male Subjects"

Dates of conduct: Jun - Oct 2014

Clinical site: Nucleus Network Limited
(The Centre for Clinical Studies)
5th Floor, Burnet Tower, AMREP Precinct,
89 Commercial Road
Melbourne, Victoria, Australia, 3004
FEI: 3008356899

ORA investigator Ms. Cynthia L. Rakestraw inspected Nucleus Network Limited, Victoria, Australia from 12/18/2017 to 12/22/2017.

The inspection included a thorough examination of study records (paper-based), subject records, the informed consent process, protocol compliance, independent ethics committee approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, Ms. Rakestraw did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Conclusion:

After reviewing the inspectional findings, I conclude the data from the audited study to be reliable. Therefore, I recommend that the data from study 20130119 (BLA 761073) be accepted for further review.

Studies of similar design conducted between the previous inspection (July, 2010) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection.

Xingfang Li, MD, RAC
Pharmacologist

Final Classification:

NAI - Nucleus Network Limited
(The Centre for Clinical Studies)
5th Floor, Burnet Tower, AMREP Precinct,
89 Commercial Road
Melbourne, Victoria, Australia, 3004
FEI: 3008356899

CC:

OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Li

Draft: XFL 02/28/2018
Edit: MFS 02/28/2018, JAK 03/03/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL SITES/Nucleus
Network Limited-The Center for Clinical Studies, Victoria,
Australia

OSIS file #: BE7590
FACTS: 11769142

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/s/

XINGFANG LI
03/05/2018

JOHN A KADAVIL
03/06/2018

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 8, 2018

TO: Julia Beaver, MD,
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Amendment to Establishment Inspection Report (EIR)
Review, covering BLA 761073, ABP 980 (proposed
biosimilar to trastuzumab) sponsored by Amgen Inc.,
USA.

Inspection Summary

The current review is to amend the previous EIR review dated on 12/19/2017 because the inspected entity, Amgen Inc., provided new stability data.

In November 2017, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073 at Amgen, Thousand Oaks, CA.

During the inspection, significant objectionable conditions were observed that impacted the reliability of the audited studies, and Form FDA 483 was issued at the inspection close-out.

Amgen responded to the issues identified. However, after evaluation of the firm's response and inspectional findings, the OSIS scientist, Hasan A. Irier Ph.D., recommended not to accept the data for Agency review unless the objectionable conditions are fully addressed.

On January 31, 2018, Amgen provided new stability data for additional freeze-thaw cycles in response to the FDA Form 483, Observation 4. The OSIS scientist reviewed the new data and found that it addressed the stability issue. However, Amgen did not provide additional data demonstrating overall inter-assay precision of the NAb assay. Therefore, this reviewer does not recommend accepting the NAb validation data for further Agency review.

Inspected Studies:

BLA 761073

Study Number: 20130119

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab(Herceptin®) in Healthy Male Subjects."

Dates of conduct: 06/14/2014 - 10/15/2014

Study Number: 20120283

Study Title: "A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer"

Dates of conduct: 04/29/2013 - 05/05/2016

Analytical site: Amgen Inc.,
720 Amgen Court, Thousand Oaks,
CA, 91320

I, Hasan A. Irier Ph.D. (OSIS), audited the analytical portion of the above studies at Amgen Inc., 720 Amgen Court, Thousand Oaks, CA, 91320 from **10/30/2017** to **11/3/2017**. At the end of the inspection, I observed objectionable conditions and issued Form FDA 483 (**Attachment 1**) to the analytical site. On November 21, 2017, Amgen Inc., provided a response to the form 483 observations (**Attachment 2**). Subsequently, I provided an evaluation of the inspectional findings and the firm's response in the EIR Review submitted on December 19, 2017. On January 31, 2018, Amgen provided additional data (**Attachment 3**) in support of freeze-thaw stability assessment of the anti-ABP980 antibody.

My evaluation of the firm's additional response specifically to OSIS's Form FDA 483 inspectional observation 4 follows:

OBSERVATION 4: Freeze and Thaw (F/T) cycle stability of the anti-drug antibody was not demonstrated during ADA validation MVR-000469.

Firm's Response: Amgen stated that to demonstrate the F/T cycle stability of the rabbit polyclonal affinity purified positive control antibody generated to ABP 980, Amgen will conduct F/T cycle stability experiments in PNHS and provide new stability data to the Agency by January 30, 2018.

OSIS Evaluation: For the stability assessment of positive control samples during ADA binding method validation, the validation report (MVR-000469, page 6 of 46) references to a separate technical report RPT-019625(**Attachment 4**). However, this report provides only a summarized list of rabbit anti-drug antibodies as either "Passed" or "Failed" for the stability testing. Furthermore, it does not provide data specifically on the freeze/thaw stability of anti-ABP 980 antibody in pooled normal human serum (PNHS). This observation was included in the form 483 issued to Amgen on November 3, 2017 (**Attachment 1**).

In their initial response sent to OSIS on November 21, 2017 (**Attachment 2**), Amgen committed to send a response to Observation 4, with data for freeze-thaw stability of anti-drug antibodies used in method validation, by January 2018.

On January 31, 2018, I received a follow-up response via e-mail with an attachment containing new data on F/T cycle stability of the anti-ABP 980 antibody that specifically addresses observation 4(**Attachment 3**). The new stability data demonstrates that at both the low and high anti-drug antibody concentration levels, the anti-ABP 980 antibody did not lose reactivity after 5 cycles of F/T in PNHS.

Conclusion:

The stability data provided by the firm as a response to Observation 4 is acceptable and adequately covers the maximum number of freeze-thaw cycles that the subject samples were subjected to during sample analysis.

However, please note that Amgen did not address the issue described in the Observations 2 (which are evaluated in the EIR Review submitted on December 19, 2017; **Attachment 5**).

Therefore, this reviewer still recommends to not to accept the immunogenicity data generated from subject sample analyses in studies 20130119 and 2012083.

Hasan Ali Irier, Ph.D.
Pharmacologist

Final Classification:

VAI Amgen Inc.,
 Thousand Oaks, CA
 FEI#: 2026154

CC:
OTS/OSIS/Kassim/Choe/Haidar/Mitchell/Fenty-Stewart/Nkah/Johnson
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Irier
OND/OHOP/DOP1/Beaver/Tilley

Draft: HAI 2/2/18
Edit: YMC 2/6/18, HAI 2/6/18, JAK 2/8/18

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/Amgen Inc.,
Thousand Oaks, CA/S-BLA 761073_ABP 980 proposed biosimilar to
trastuzumab

OSIS File #: BE 7590

FACTS: 11769182

ATTACHMENTS

Attachment 1. ABP980_Amgen_Form FDA 483-Signed

Attachment 2. 112082017_BLA 761073_Amgen 483 Response

Attachment 3. Amgen_Thousand Oaks_Follow-up Response to Form 483
Observation 4

Attachment 4. RPT-019625-Immunoglobulin-Stability

Attachment 5. EIR Review Amgen-Thousand Oaks_12-19-17-signed.pdf

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 19, 2017

TO: Geoffrey S. Kim, MD
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of bioanalytical Establishment Inspection
Report (EIR), covering BLA 761073, ABP 980 (proposed
biosimilar to trastuzumab) sponsored by Amgen Inc.,
USA.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073 at Amgen, Thousand Oaks, CA.

Form FDA 483 was issued at the inspection close-out. Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited studies. The firm provided a response to the form 483 observations on November 21, 2017. The final inspection classification is Voluntary Action Indicated (VAI).

In the form 483 response, Amgen stated that additional method validation data (freeze-thaw stability of anti-drug antibodies used in method validation) will be provided by January 2018. Additionally, the firm's response did not address deficiencies in the overall inter-assay precision of the NAb assay. Thus, pending the receipt and evaluation of additional method validation data, I recommend that the data from studies 20130119

and 2012083 not be accepted for further Agency review. Upon receipt, OSIS will evaluate the additional method validation data, and amend this EIR Review.

The current EIR Review provides evaluation of inspectional findings and the firm's response to form 483 observations.

Inspected Studies:

BLA 761073

Study Number: 20130119

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab(Herceptin®) in Healthy Male Subjects."

Dates of conduct: 06/14/2014 - 10/15/2014

Study Number: 20120283

Study Title: "A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer"

Dates of conduct: 04/29/2013 - 05/05/2016

Analytical site: Amgen Inc.,
720 Amgen Court, Thousand Oaks,
CA, 91320

OSIS scientist Hasan A. Irier audited the analytical portion of the above studies at Amgen Inc., 720 Amgen Court, Thousand Oaks, CA, 91320 from **10/30/2017** to **11/3/2017**.

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the end of the inspection, I observed objectionable conditions and issued Form FDA 483 to the analytical site. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated November 21, 2017 (**Attachment 2**), and my evaluation are presented below.

OBSERVATION 1: Expired reagents used during anti-ABP 980 antibody (ADA) and Neutralizing antibody (NAb) method validation experiments in support of studies 2030119 and 20120283. Specifically,

1.a. Herceptin-EU (lot#H4009, expiration date 8/31/2015) used during ABP 980 cross reactivity to Herceptin-US and Herceptin-EU in NAb validation experiment (Notebook# (b) (4)) conducted on (b) (4).

1.b. Pooled Normal Human Serum (PNHS) (lot # BRH701482, expiration date 4/2/2013) used during validation of Lower Limit of Reliable Detection (LLRD) concentrations of 80 ng/ml anti-ABP 980 in donor samples (Notebook # (b) (4)) conducted on (b) (4).

Firm's Response: The firm acknowledged the use of expired reagents and provided clarification and additional information for the expiration status of specific reagents listed in observations 1a and 1b. Specifically, Amgen stated that the expiration date of the PNHS lot # BRH701482 (Observation **1b**) was incorrectly recorded as April 2 2013, instead of April 2, 2018, and provided the certificate of analysis in the response (**Attachment 2, Figure 1**). Amgen also stated that the notebooks were corrected and the COA of the PNHS are referenced and included with the original notebook records.

For Observation **1a**, Amgen acknowledged the use of Herceptin-EU during NAb validation experiments 10 days after the Herceptin-EU expired. Amgen presented cross-reactivity experiment results in their response (**Attachment 2, Table 1**) to demonstrate comparable signal depletion of ABP 980 and Herceptin-EU in cross reactivity experiment. Amgen stated that as a corrective action, SOPs for binding and neutralizing antibody assay validation were updated to ensure that expired reagents will not be used during method validation experiments and study sample analyses.

OSIS Evaluation: Use of expired reagents in validation experiments is discouraged in immunogenicity studies. Amgen has taken corrective actions to prevent the use of expired agents during method validation experiments and study sample analysis.

Given the acceptable results from the validation of LLRD and comparable cross-reactivity results between ABP 980 and Herceptin-EU in the NAb assay, this observation will not have a significant impact on study outcome.

OBSERVATION 2: Global assay precision assessment did not include failed validation runs during Neutralizing antibody (NAb) assay validation (MVR-000470) for ABP 980 and Herceptin-EU. Inclusion of failed runs in global assay precision resulted in assay precision not meeting the acceptance criteria.

Firm's Response: Amgen acknowledges that four failed runs were not included in global precision (defined as "inter-assay precision") calculations during method validation. However, Amgen disagrees that all failed runs should be included in calculations of method precision. In the response, Amgen provided a list of all passing and failed runs used for calculating overall inter-assay precision of the NAb Assay (**Attachment 2, Table 4**). In Table 4, Amgen identifies three of the four failed runs as failed due to "Technical Error" during the conduct of experiment, and the fourth run as failed due to not meeting pre-defined acceptance criteria of positive control ratios during the confirmatory assay. Amgen re-calculated the overall inter-assay precision of assay control ratios by only including one of the failed runs (the failure was due to %CV criteria that was not met for the positive controls) and presented the new data in the response (**Attachment 2, Table 3**). Amgen states that the recalculated results with the failed run meets pre-defined acceptance criteria for overall inter-assay precision. Amgen also stated that binding and neutralizing antibody assay validation report templates will be updated to include a list of failed runs and reason for their failure.

OSIS Evaluation: Amgen uses an analytical method (MET-003419) and follows protocol (MVP-00299) and SOP-000032 for detection of neutralizing antibodies against ABP 980. As described in their SOP-000032 "Validation of Assays Used for the Detection of Anti-Drug Neutralizing Antibodies" (**Attachment 3**), Amgen determines inter-assay precision from assays performed over at least 3 different days with at least 2 analysts. The inter-assay precision is assessed by analyzing ratios involving positive controls, or PC (e.g. DC/PC, PC/DC) as defined in MVP-00299 for all passing validation experiments. For a validation experiment to be accepted as "passed", Amgen uses (b) (4)

[REDACTED]

In their response, Amgen provided a list of all runs (including the four failed runs) used for calculating overall inter-assay precision of the NAb Assay (**Attachment 2, Table 4**). In this list, the reason for three of the failed runs (identified as "Other Serum Interference", 24-Oct-2014, Assay Number 23, Runs 1, 2 and 3) was "Technical Error" with no further information.

During the current inspection, Amgen also provided a similar list of passed and failed runs for the NAb assay (**Attachment 4**). However, in the list provided during the inspection, the same three runs ("Other Serum Interference", 24-Oct-2014, Assay Number 23, Runs 1, 2 and 3) were identified as failed runs because of the DC/PC failure (a pre-defined acceptance criteria of positive control ratios during the confirmatory assay) instead of "Technical Error" as stated in their response. Additionally, when I had requested Amgen to include these three failed runs in the calculation of overall inter-assay precision during the inspection, it resulted in a %CV DC/PC of 38% (acceptance criteria is $\leq 25\%$). Therefore, the overall inter-assay precision did not meet acceptance criteria for the NAb method (**Attachment 5**, see D/C values in ABP 980_All Runs vs. ANBP980_Passing Runs). The discrepancy between the run lists provided during the inspection and in the firm's 483 response should be addressed by Amgen. Until Amgen provides clarification on the discrepancy between the two assay run lists, and provides additional data demonstrating overall inter-assay precision of the NAb assay, OSIS does not recommend accepting the NAb validation data for further Agency review.

OBSERVATION 3: The results of anti-ABP980 antibody assessment of subject samples from study 20120283 show that the Low Positive Controls (LPC) do not confirm in the confirmatory assay.

Firm's Response: Amgen responded that the concentration of the low positive control (LPC) was statistically determined to allow for a 1% assay rejection rate based on the data generated during the validation of the anti-ABP980 binding anti-drug antibody (ADA) method (MVR-00469). They stated that this approach follows the recommendations in the 2009 and 2016 FDA Draft Guidance for Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Amgen stated that during subject sample analysis, 2 out of 139 total plates (1.4 %) failed to pass the screening assay acceptance criteria because the LPC values were below the assay cut point. In the confirmatory assay, 5 out of 29 plates (17 %) failed to pass confirmatory assay acceptance criteria because the LPC from drug-treated samples were below assay cut point.

OSIS Evaluation: Amgen acknowledges that in the confirmatory assay of LPC, 17% fail rate is higher than expected given that the screening assay fail rate is 1.4%. However, LPC concentration was low enough to detect any loss of assay sensitivity during sample analysis, and all samples that failed to pass acceptance criteria were re-analyzed and final ADA results demonstrated acceptable inhibition of the LPC signal to

noise ratio. Therefore, there is no impact on the validity of data generated from the anti-ABP 980 antibody sample results for study 20120183. This observation will not have a significant impact on study outcome.

OBSERVATION 4: Freeze and Thaw (F/T) cycle stability of the anti-drug antibody (ADA) was not demonstrated during ADA Method Validation MVR-000469

Firm's Response: Amgen stated that to demonstrate the F/T cycle stability of the rabbit polyclonal affinity purified positive control antibody generated to ABP 980, Amgen will conduct F/T cycle stability experiments in PNHS and provide new stability data to the Agency by January 30, 2018.

OSIS Evaluation: After Amgen provides data on F/T cycle stability experiments, OSIS will review the data and provide recommendation in an amendment to the current EIR Review.

Conclusion:

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, I recommend that the immunogenicity data (ADA and NAb studies) from studies 20130119 and 2012083 not be accepted for Agency review. OSIS has determined that the objectionable conditions identified in Observations 2 and 4 for the NAb and ADA method validations should be fully addressed by Amgen to ensure the reliability of the immunogenicity data generated from subject sample analyses in studies 20130119 and 2012083.

Hasan Ali Irier, Ph.D.
Pharmacologist

Final Classification:

VAI Amgen Inc.,
 Thousand Oaks, CA
 FEI#: 2026154

CC:

OTS/OSIS/Kassim/Choe/Haidar/Fenty-Stewart/Nkah/Johnson

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Irier

Draft: HAI 12/12/17

Edit: JAK 12/13/17

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/Amgen Inc., Thousand Oaks, CA/S-BLA 761073_ABP 980 proposed biosimilar to trastuzumab

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881532400>

OSIS File #: BE 7590

FACTS: 11769182

ATTACHMENTS

Attachment 1. ABP980_Amgen_Form FDA 483-Signed

Attachment 2. 112082017_BLA 761073_Amgen 483 Response

Attachment 3. SOP-000032

Attachment 4. Request 53 NAb Method Validation Assay Pass Fail Summary

Attachment 5. Regulatory Request_72 NAb Method Validation

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/s/

HASAN A IRIER

02/08/2018

This EIR Review is an amendment to the previous EIR review dated on 12/19/2017 because the inspected entity, Amgen Inc., provided new stability data.

JOHN A KADAVIL

02/08/2018

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 1/3/2018

TO: Office of New Drug
Division of Oncology Products (DOP1)

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: BLA 761073

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

ANGEL S JOHNSON
01/04/2018

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 19, 2017

TO: Geoffrey S. Kim, MD
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of bioanalytical Establishment Inspection
Report (EIR), covering BLA 761073, ABP 980 (proposed
biosimilar to trastuzumab) sponsored by Amgen Inc.,
USA.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073 at Amgen, Thousand Oaks, CA.

Form FDA 483 was issued at the inspection close-out. Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited studies. The firm provided a response to the form 483 observations on November 21, 2017. The final inspection classification is Voluntary Action Indicated (VAI).

In the form 483 response, Amgen stated that additional method validation data (freeze-thaw stability of anti-drug antibodies used in method validation) will be provided by January 2018. Additionally, the firm's response did not address deficiencies in the overall inter-assay precision of the NAb assay. Thus, pending the receipt and evaluation of additional method validation data, I recommend that the data from studies 20130119

and 2012083 not be accepted for further Agency review. Upon receipt, OSIS will evaluate the additional method validation data, and amend this EIR Review.

The current EIR Review provides evaluation of inspectional findings and the firm's response to form 483 observations.

Inspected Studies:

BLA 761073

Study Number: 20130119

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab(Herceptin®) in Healthy Male Subjects."

Dates of conduct: 06/14/2014 - 10/15/2014

Study Number: 20120283

Study Title: "A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer"

Dates of conduct: 04/29/2013 - 05/05/2016

Analytical site: Amgen Inc.,
720 Amgen Court, Thousand Oaks,
CA, 91320

OSIS scientist Hasan A. Irier audited the analytical portion of the above studies at Amgen Inc., 720 Amgen Court, Thousand Oaks, CA, 91320 from **10/30/2017** to **11/3/2017**.

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the end of the inspection, I observed objectionable conditions and issued Form FDA 483 to the analytical site. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated November 21, 2017 (**Attachment 2**), and my evaluation are presented below.

OBSERVATION 1: Expired reagents used during anti-ABP 980 antibody (ADA) and Neutralizing antibody (NAb) method validation experiments in support of studies 2030119 and 20120283. Specifically,

1.a. Herceptin-EU (lot#H4009, expiration date 8/31/2015) used during ABP 980 cross reactivity to Herceptin-US and Herceptin-EU in NAb validation experiment (Notebook# (b) (4)) conducted on (b) (4).

1.b. Pooled Normal Human Serum (PNHS) (lot # BRH701482, expiration date 4/2/2013) used during validation of Lower Limit of Reliable Detection (LLRD) concentrations of 80 ng/ml anti-ABP 980 in donor samples (Notebook # (b) (4)) conducted on (b) (4).

Firm's Response: The firm acknowledged the use of expired reagents and provided clarification and additional information for the expiration status of specific reagents listed in observations 1a and 1b. Specifically, Amgen stated that the expiration date of the PNHS lot # BRH701482 (Observation **1b**) was incorrectly recorded as April 2 2013, instead of April 2, 2018, and provided the certificate of analysis in the response (**Attachment 2, Figure 1**). Amgen also stated that the notebooks were corrected and the COA of the PNHS are referenced and included with the original notebook records.

For Observation **1a**, Amgen acknowledged the use of Herceptin-EU during NAb validation experiments 10 days after the Herceptin-EU expired. Amgen presented cross-reactivity experiment results in their response (**Attachment 2, Table 1**) to demonstrate comparable signal depletion of ABP 980 and Herceptin-EU in cross reactivity experiment. Amgen stated that as a corrective action, SOPs for binding and neutralizing antibody assay validation were updated to ensure that expired reagents will not be used during method validation experiments and study sample analyses.

OSIS Evaluation: Use of expired reagents in validation experiments is discouraged in immunogenicity studies. Amgen has taken corrective actions to prevent the use of expired agents during method validation experiments and study sample analysis.

Given the acceptable results from the validation of LLRD and comparable cross-reactivity results between ABP 980 and Herceptin-EU in the NAb assay, this observation will not have a significant impact on study outcome.

OBSERVATION 2: Global assay precision assessment did not include failed validation runs during Neutralizing antibody (NAb) assay validation (MVR-000470) for ABP 980 and Herceptin-EU. Inclusion of failed runs in global assay precision resulted in assay precision not meeting the acceptance criteria.

Firm's Response: Amgen acknowledges that four failed runs were not included in global precision (defined as "inter-assay precision") calculations during method validation. However, Amgen disagrees that all failed runs should be included in calculations of method precision. In the response, Amgen provided a list of all passing and failed runs used for calculating overall inter-assay precision of the NAb Assay (**Attachment 2, Table 4**). In Table 4, Amgen identifies three of the four failed runs as failed due to "Technical Error" during the conduct of experiment, and the fourth run as failed due to not meeting pre-defined acceptance criteria of positive control ratios during the confirmatory assay. Amgen re-calculated the overall inter-assay precision of assay control ratios by only including one of the failed runs (the failure was due to %CV criteria that was not met for the positive controls) and presented the new data in the response (**Attachment 2, Table 3**). Amgen states that the recalculated results with the failed run meets pre-defined acceptance criteria for overall inter-assay precision. Amgen also stated that binding and neutralizing antibody assay validation report templates will be updated to include a list of failed runs and reason for their failure.

OSIS Evaluation: Amgen uses an analytical method (MET-003419) and follows protocol (MVP-00299) and SOP-000032 for detection of neutralizing antibodies against ABP 980. As described in their SOP-000032 "Validation of Assays Used for the Detection of Anti-Drug Neutralizing Antibodies" (**Attachment 3**), Amgen determines inter-assay precision from assays performed over at least 3 different days with at least 2 analysts. The inter-assay precision is assessed by analyzing ratios involving positive controls, or PC (e.g. DC/PC, PC/DC) as defined in MVP-00299 for all passing validation experiments. For a validation experiment to be accepted as "passed", Amgen uses (b) (4)

[REDACTED]

In their response, Amgen provided a list of all runs (including the four failed runs) used for calculating overall inter-assay precision of the NAb Assay (**Attachment 2, Table 4**). In this list, the reason for three of the failed runs (identified as "Other Serum Interference", 24-Oct-2014, Assay Number 23, Runs 1, 2 and 3) was "Technical Error" with no further information.

During the current inspection, Amgen also provided a similar list of passed and failed runs for the NAb assay (**Attachment 4**). However, in the list provided during the inspection, the same three runs (“Other Serum Interference”, 24-Oct-2014, Assay Number 23, Runs 1, 2 and 3) were identified as failed runs because of the DC/PC failure (a pre-defined acceptance criteria of positive control ratios during the confirmatory assay) instead of “Technical Error” as stated in their response. Additionally, when I had requested Amgen to include these three failed runs in the calculation of overall inter-assay precision during the inspection, it resulted in a %CV DC/PC of 38% (acceptance criteria is $\leq 25\%$). Therefore, the overall inter-assay precision did not meet acceptance criteria for the NAb method (**Attachment 5**, see D/C values in ABP 980_All Runs vs. ANBP980_Passing Runs). The discrepancy between the run lists provided during the inspection and in the firm’s 483 response should be addressed by Amgen. Until Amgen provides clarification on the discrepancy between the two assay run lists, and provides additional data demonstrating overall inter-assay precision of the NAb assay, OSIS does not recommend accepting the NAb validation data for further Agency review.

OBSERVATION 3: The results of anti-ABP980 antibody assessment of subject samples from study 20120283 show that the Low Positive Controls (LPC) do not confirm in the confirmatory assay.

Firm’s Response: Amgen responded that the concentration of the low positive control (LPC) was statistically determined to allow for a 1% assay rejection rate based on the data generated during the validation of the anti-ABP980 binding anti-drug antibody (ADA) method (MVR-00469). They stated that this approach follows the recommendations in the 2009 and 2016 FDA Draft Guidance for Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Amgen stated that during subject sample analysis, 2 out of 139 total plates (1.4 %) failed to pass the screening assay acceptance criteria because the LPC values were below the assay cut point. In the confirmatory assay, 5 out of 29 plates (17 %) failed to pass confirmatory assay acceptance criteria because the LPC from drug-treated samples were below assay cut point.

OSIS Evaluation: Amgen acknowledges that in the confirmatory assay of LPC, 17% fail rate is higher than expected given that the screening assay fail rate is 1.4%. However, LPC concentration was low enough to detect any loss of assay sensitivity during sample analysis, and all samples that failed to pass acceptance criteria were re-analyzed and final ADA results demonstrated acceptable inhibition of the LPC signal to

noise ratio. Therefore, there is no impact on the validity of data generated from the anti-ABP 980 antibody sample results for study 20120183. This observation will not have a significant impact on study outcome.

OBSERVATION 4: Freeze and Thaw (F/T) cycle stability of the anti-drug antibody (ADA) was not demonstrated during ADA Method Validation MVR-000469

Firm's Response: Amgen stated that to demonstrate the F/T cycle stability of the rabbit polyclonal affinity purified positive control antibody generated to ABP 980, Amgen will conduct F/T cycle stability experiments in PNHS and provide new stability data to the Agency by January 30, 2018.

OSIS Evaluation: After Amgen provides data on F/T cycle stability experiments, OSIS will review the data and provide recommendation in an amendment to the current EIR Review.

Conclusion:

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, I recommend that the immunogenicity data (ADA and NAb studies) from studies 20130119 and 2012083 not be accepted for Agency review. OSIS has determined that the objectionable conditions identified in Observations 2 and 4 for the NAb and ADA method validations should be fully addressed by Amgen to ensure the reliability of the immunogenicity data generated from subject sample analyses in studies 20130119 and 2012083.

Hasan Ali Irier, Ph.D.
Pharmacologist

Final Classification:

VAI Amgen Inc.,
 Thousand Oaks, CA
 FEI#: 2026154

CC:

OTS/OSIS/Kassim/Choe/Haidar/Fenty-Stewart/Nkah/Johnson

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Irier

Draft: HAI 12/12/17

Edit: JAK 12/13/17

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/Amgen Inc., Thousand Oaks, CA/S-BLA 761073_ABP 980 proposed biosimilar to trastuzumab

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881532400>

OSIS File #: BE 7590

FACTS: 11769182

ATTACHMENTS

Attachment 1. ABP980_Amgen_Form FDA 483-Signed

Attachment 2. 112082017_BLA 761073_Amgen 483 Response

Attachment 3. SOP-000032

Attachment 4. Request 53 NAb Method Validation Assay Pass Fail Summary

Attachment 5. Regulatory Request_72 NAb Method Validation

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/s/

HASAN A IRIER
12/19/2017

JOHN A KADAVIL
12/19/2017