

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761074Orig1s000

PRODUCT QUALITY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: November 20, 2017
To: Administrative File, STN 761074\0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 2062
Applicant: Mylan GmbH
Facility: [REDACTED] (b) (4)
Product: MYL-1401O, Ogivri ((proposed biosimilar to Herceptin® trastuzumab),
Dosage: Lyophilized powder (440mg) in a multi-use vial for intravenous infusion
Indication: For the treatment of HER2 overexpressing breast cancer, metastatic gastric cancer or gastroesophageal junction adenocarcinoma
Due Date: December 03, 2017

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY: This addendum includes review of the post inspection modifications performed on the [REDACTED] (b) (4) which include [REDACTED] (b) (4). [REDACTED] (b) (4) study report are submitted in amendment (sequence number 0047) dated September 19, 2017. Media fill validation study reports are submitted in amendment (sequence number 0052) dated November 01, 2017. Applicant's response (sequence number 0053) to the information request was also reviewed.

INTRODUCTION:

As a follow-up commitment to the Agency's 483-observation during the inspection conducted on [REDACTED] (b) (4)

ASSESSMENTS:

The following information request was communicated to the applicant on September 14, 2017 to update the BLA application with the changes made in the [REDACTED] (b) (4) in response to the Agency's 483-observation.

Satisfactory

3.2.P.8 STABILITY

Section 3.2.P.8, Stability was updated with data from 18 month stability time point for BWFI at the recommended storage condition of $5\pm 3^{\circ}\text{C}$. CCI test results performed at 18 month time point met the acceptance criteria.

Reviewer's comments: Only microbiological test results of the stability data was reviewed.

Conclusion

- I. The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective
- II. This information regarding the media fill qualification runs was reviewed in entirety by DMA.
- III. See Panorama for the compliance status of the drug product manufacturing site.

Information requests sent out during the review cycle

1. Please provide a comparison of the qualified media fill parameters, number of vials filled, fill speed, and duration of filling with those will be used for routine manufacturing of MYL-1401O drug product

2.  (b) (4)

3.

4.



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 11/28/2017 10:08:00AM
GUID: 508da7160002976791592556d218b997



Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 11/28/2017 11:07:35AM
GUID: 508da717000297bcbfce0919f8c09594



First Biosimilar trastuzumab

Recommendation: Approval

**BLA 761074
Review**

Date: November 22, 2017

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

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

Drug Name/Dosage Form	Ogivri (trastuzumab-dkst)/ for injection
Strength/Potency	420 mg/vial
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Indication	Treatment of HER2-overexpressing breast cancer
Applicant/Sponsor	Mylan GmbH
US agent, if applicable	Mylan Pharmaceuticals Inc.

Product Overview

Ogivri (trastuzumab-dkst) is a proposed biosimilar to US-Herceptin (trastuzumab). It is a humanized afucosylated IgG1κ monoclonal antibody produced in CHO cells. Trastuzumab targets human epidermal growth factor receptor 2 (HER2) and when bound to HER2 on HER2-expressing cells, trastuzumab 1) inhibits HER2 receptor dimerization, 2) increases destruction of the endocytic portion of the HER2 receptor 3) inhibits HER2 extracellular domain shedding, and 4) activates cell-mediated immune defenses such as ADCC activity through concomitant binding to Fcγ receptors on immune effector cells. Ogivri drug product is supplied at 420 mg/vial as a sterile, lyophilized powder for intravenous infusion; the 420 mg presentation is a multi-dose vial. Ogivri is proposed as a treatment for HER2 overexpressing breast cancer.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Kristen Nickens	DBRR I/OBP/OPQ
Drug Product	Kristen Nickens	DBRR I/OBP/OPQ
Analytical Similarity	Kristen Nickens	DBRR I/OBP/OPQ
Immunogenicity	Brian Janelsins	DBRR I/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks	DIA/OPF/OPQ
Microbiology (DP)	Lakshmi Narasimhan	DMA/OPF/OPQ
Microbiology (DS)	Reyes Candau-Chacon	DMA/OPF/OPQ
Business Process Manager	Keith Olin	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Sarah Kennett	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Kathleen Clouse	DBRR I/OBP/OPQ
Tertiary Reviewer for Analytical Similarity	Emanuela Lacana	OBP/OPQ
Microbiology Team Lead	Patricia Hughes	DMA/OPF/OPQ DMA/OPF/OPQ
Facilities Team Lead	Zhihao Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Charlene Wheeler	DOPI/OHOP/OND
Cross-disciplinary Team Lead	Laleh Amiri Kordestani	DOPI/OHOP/OND
Medical Officer	Suparna Wedman, Jennifer Gao	DOPI/OHOP/OND
Pharm/Tox	Haw-Jyh Chiu/Todd Palmby (TL)	DOPI/OHOP/OND
Clinical Pharmacology	Brian Furmanski/Sarah Schrieber (TL)	DOPI/OHOP/OND
Stats	Lijun Zhang/Shenghui Tang (TL)	OB/DBV
CMC Stats	Li Xing/Meiyu Shen/Yi Tsong (TL)	OB/DBIV

a. Names

- i. Proprietary Name: Ogivri
- ii. Trade Name: Ogivri
- iii. Non-Proprietary/USAN: trastuzumab-dkst
- iv. CAS name: 180288-69-1
- v. INN Name: trastuzumab
- vi. OBP systematic name: MAB HUMANIZED (IGGI) ANTI P04626 (ERBB2_HUMAB) [MYL-1401O]

b. Pharmacologic category: HER2/neu receptor antagonist

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Branch Chief	Reyes Candau-Chacon for Patricia Hughes	See Panorama
Facilities Branch Chief	Zhihao Peter Qiu	See Panorama
Director OBP/DBRR I	Kathleen Clouse	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761074/0000	11/3/16	OBP, DIA, DMA
761074/0006	12/19/16	OBP, DMA
761074/0008	12/21/16	OBP, DMA, DIA
761074/0009	1/3/17	DMA
761074/0010	1/6/17	OBP
761074/0013	1/13/17	OBP
761074/0015	1/23/17	DMA
761074/0017	2/10/17	OBP
761074/0018	2/21/17	OBP
761074/0021	4/11/17	OBP
761074/0022	4/20/17	DMA
761074/0024	4/24/17	DMA
761074/0026	5/8/17	DMA
761074/0028	5/12/17	OBP
761074/0029	5/15/17	DMA
761074/0030	5/16/17	OBP
761074/0036	6/20/17	OBP
761074/0037	6/23/17	OBP
761074/0041	7/26/17	OBP
761074/0043	7/26/17	DMA
761074/0044	7/28/17	OBP
761074/0045	7/31/17	OBP
761074/0046	8/4/17	DMA
761074/0047	9/18/2017	DMA
761074/0048	9/20/2017	OBP
761074/0049	10/4/2017	OBP
761074/0050	10/23/2017	OBP
761074/0052	11/1/2017	OBP, DMA
761074/0053	11/20/2017	DMA

B. DMFs:

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

(b) (4)	(b) (4)	(b) (4)	3	N/A
	(b) (4)		3	N/A
	(b) (4)		1	N/A
	(b) (4)		3	N/A
	(b) (4)		3	N/A
	(b) (4)		3	N/A

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

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

C. Other Documents: None

3. CONSULTS: None

Product Quality Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761074 for trastuzumab-dkst, manufactured by Mylan GmbH. The data submitted in this application are adequate to support the conclusion that the manufacture of trastuzumab-dkst is well controlled and leads to a product that is pure and potent. We recommend that trastuzumab-dkst be approved for human use under the conditions specified in the package insert.

b. Action Letter Language:

- Manufacturing locations:
 - Drug Substance:
 - Manufacturing: (b) (4)
 - Drug Product:
 - Manufacturing, fill, labeling and packaging: (b) (4)
 - Bacteriostatic Water for Injection (BWFI):
 - Manufacturing, fill, labeling and packaging: Biocon Limited, Bangalore, India
- Fill size and dosage form
 - Trastuzumab-dkst: 420 mg/vial for injection, multi-dose vial
 - BWFI: 20 mL/vial
- Dating period:
 - Drug Product: 48 months when stored at 2-8°C
 - Drug Substance: (b) (4) months when stored at (b) (4) °C
 - Packaged component:
 - BWFI: 18 months when stored at (b) (4) °C
 - Stability Option:
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and BWFI under 21 CFR 601.12.
- Exempt from lot release:
 - Yes. Trastuzumab-dkst is a specified product exempted according to 21 CFR 601.2a.

c. Benefit/Risk Considerations

Ogivri (trastuzumab-dkst) is proposed as a biosimilar to US-Herceptin (trastuzumab) for treatment of HER2 overexpressing breast cancer. Multiple mechanisms of action have been proposed for trastuzumab, which targets

human epidermal growth factor receptor 2 (HER2.) The mechanisms of action include inhibition of HER2 signaling through the receptor and subsequent cell proliferation, adhesion, and differentiation through inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, and inhibition of extracellular domain shedding. Activation of cell-mediated immune defenses, such as antibody-dependent cellular cytotoxicity (ADCC) activity, has also been identified as a mechanism of action of trastuzumab; it appears that natural killer (NK) cells are important mediators of ADCC activity in the context of trastuzumab-treated breast cancer.

With respect to analytical similarity, Ogivri was evaluated and compared to US-Herceptin and EU-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action (see Table 4, in Section D, Analytical Similarity, below). The analytical data submitted support the conclusion that Ogivri is highly similar to US-Herceptin. The amino acid sequences of Ogivri and US-Herceptin are identical. A comparison of the secondary and tertiary structures and the impurity profiles of Ogivri and US-Herceptin support the conclusion that the two products are highly similar. HER2 binding, inhibition of proliferation, and ADCC activity, which reflect the presumed primary mechanisms of action of US-Herceptin, were determined to be equivalent. Some tests indicate that subtle shifts in glycosylation [e.g., sialic acid, high mannose, and non-glycosylated heavy chain (NG-HC)] exist and are likely an intrinsic property of Ogivri due to the manufacturing process. High mannose and sialic acid containing glycans can impact PK, while NG-HC is associated with loss of effector function through reduced FcγRIIIa binding and reduced ADCC activity. However, FcγRIIIa binding was similar among products and ADCC activity was equivalent among products. The residual uncertainties related to the increases in total mannose forms and sialic acid and decreases in NG-HC were addressed by the ADCC similarity and by the PK similarity between Ogivri and US-Herceptin as concluded by the clinical review team. Additional subtle differences in size and charge related variants were detected; however, these variants generally remain within the quality range criteria. Further, the data submitted by the applicant support the conclusion that Ogivri and US-Herceptin can function through the same mechanisms of action for the indications for which Herceptin is currently approved, to the extent that the mechanisms of action are known or can reasonably be determined. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, Ogrivi is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. In addition, the three pairwise comparisons of Ogivri, US-Herceptin and EU-Herceptin established the analytical component of the scientific bridges among the three products to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-Herceptin to support a demonstration of biosimilarity of Ogivri to US-Herceptin.

The overall control strategy for Ogrivi manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of Drug Substance (DS) and Drug Product (DP), and stability of these materials. There were numerous issues with the DS and DP control strategy that were resolved during the review cycle through communication with the applicant and a significant number of corrections to the BLA and updates and

additions to the control strategy. The current proposed manufacturing control strategy, in-process controls, process monitoring tests, release, and stability testing as presented in the BLA is sufficient to ensure process consistency and DS and DP that have appropriate quality and are free of adventitious agents.

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

1. Perform a method validation study to confirm the suitability of the FcγRIIIa-V158 surface plasmon resonance (SPR) binding assay for use as a potency assay for drug substance and drug product lot release and stability testing. The final study results will be submitted to the BLA.



II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance, final bulk, and drug product.

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

Table 1: Drug Substance (DS) and Drug Product (DP) CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
HER2 binding (potency)	Efficacy	Intrinsic to the molecule. Impacted by aggregation, and fragmentation and potentially deamidation. Minimal change is expected during storage through expiry.	(b) (4)	N/A
Inhibition of proliferation (potency)	Efficacy	Intrinsic to the molecule. Impacted by aggregation, and fragmentation and potentially deamidation. Minimal change is expected during storage through expiry.		N/A
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation and fragmentation and potentially deamidation Minimal change is expected during storage through expiry.		No CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A

High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Efficacy (HER2 binding and ADCC), Safety/Immunogenicity and potentially PK	Manufacturing process and exposure to heat. Minimal change is expected during storage under recommended conditions through expiry.	(b) (4)	N/A
Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat and light stress. Minimal increase in fragments is expected during storage under recommended conditions.		N/A
Glycosylation (afucosylated species)	Efficacy (ADCC activity/FcγRIIIa binding)	Cell culture process No change is expected during storage.		N/A

			(b) (4)	
Glycosylation (high mannose)	PK and efficacy (afucosylated)	Cell culture process No change is expected during storage.		N/A
Light chain Asn30 deamidation	Efficacy; not well characterized (deamidation at some sites may also impact PK)	Manufacturing process and exposure to heat. Minimal change is expected during storage under recommended conditions.		Deamidation at this and other sites not well characterized. Acidic species have lower potency.
Heavy Chain Met255 and Met431 oxidation	Not well characterized; potentially PK (FcRn binding)	Manufacturing process and potentially exposure to heat and light stress (b) (4) [Redacted]. Minimal change is expected under recommended storage conditions.		Oxidation at M255 appears to require significant stress. M431 not well characterized.
Heavy Chain Asp102 isomerization	Efficacy	Manufacturing process including hold, storage, exposure to heat.		Not well characterized.



Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		(b) (4) N/A
pH	Safety and Efficacy	Formulation		N/A
Protein Content	Efficacy	Manufacturing process		N/A
PEG 3350	Safety and efficacy (control of degradation)	Formulation		N/A

**B. Drug Substance [trastuzumab] 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	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4)	Safety and Immunogenicity	Process related impurity (b) (4)		N/A
(Process-related				

impurity)			(b) (4)	
(b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (6)		Evaluated by pharm/tox review team also.
(b) (4) (Process-related impurity)	Safety, immunogenicity	Cell bank (b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations via raw materials		N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be		N/A

		introduced during cell culture operations.		
Leachables (Process-related impurity)	Safety	Manufacturing components and the DS container closure system	(b) (4)	N/A
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through raw materials and throughout the manufacturing process		N/A

a. Description

Trastuzumab-dkst is a recombinant, humanized IgG1 κ monoclonal antibody and consists of two heavy chains that are each composed of 450 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 300 (Asn300). The molecular weight of trastuzumab-dkst without C-terminal lysine is 148,054 Da.

The theoretical extinction coefficient was calculated to be 1.48 (mg/mL)⁻¹ cm⁻¹, and it was determined experimentally to be 1.47 (mg/mL)⁻¹ cm⁻¹. The theoretical value has been used during development and will continue to be used to determine the trastuzumab-dkst protein concentration for commercial use.

b. Mechanism of action

Multiple mechanisms of action have been proposed for trastuzumab, which binds to HER2. The mechanisms of action include inhibition of HER2 signaling through the receptor and subsequent cell proliferation, adhesion, and differentiation through inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, and inhibition of extracellular domain shedding. Activation of cell-mediated immune defenses, such as ADCC activity, through concomitant binding to HER2 and to Fc γ receptors on immune effector cells has also been identified as a mechanism of action of trastuzumab. It appears that NK cells are important mediators of ADCC activity in the context of trastuzumab-treated breast cancer. Complement-dependent cytotoxicity (CDC) is not considered to be a major mechanism of action for trastuzumab.

c. Potency Assays

HER2 binding is assessed using a cell-based flow cytometry assay. HER2-expressing SKBR3 cells are incubated with a series of concentrations of sample. During the incubation, the antibody binds to the HER2 expressed on the SKBR3 cell surface. The samples are then incubated with anti-human IgG1 FITC conjugated-Fc specific secondary antibody, which recognizes any antibody bound to the SKBR3 cells. The cells are processed through the flow cytometer, and the mean fluorescent intensity of the gated cell population is recorded and used to calculate the amount of HER2 bound antibody normalized to the reference material (RM) and plotted using PLA software. The HER2 binding value is reported as relative potency.

Inhibition of proliferation is determined using a SKBR3-cell based bioassay. SKBR3 cells are seeded onto poly-L-lysine coated culture plates and incubated with serial dilutions of samples for 5 days. After 5 days, the samples are incubated with alamarBlue fluorescent detection reagent to allow for the detection of metabolically active cells. The relative fluorescence of samples is normalized to the corresponding RM value. The results are reported as relative potency determined by the geometric mean of the potency ratios.

ADCC activity is evaluated using a cell-based assay employing SKBR3 breast cancer cells as target cells and peripheral blood mononuclear cells (PBMC) as effector cells. SKBR3 cells are seeded and pre-incubated with serial dilutions of sample to allow for binding of the antibody to the target cell line. Isolated PBMCs are then incubated with the sample to allow the PBMC effector cells to form a complex with the antibody bound SKBR3 cells and initiate cell killing through ADCC activity. To quantify ADCC activity, Cyto-Tox Glo luminescence reagent, which detects proteases release from dead cells, is

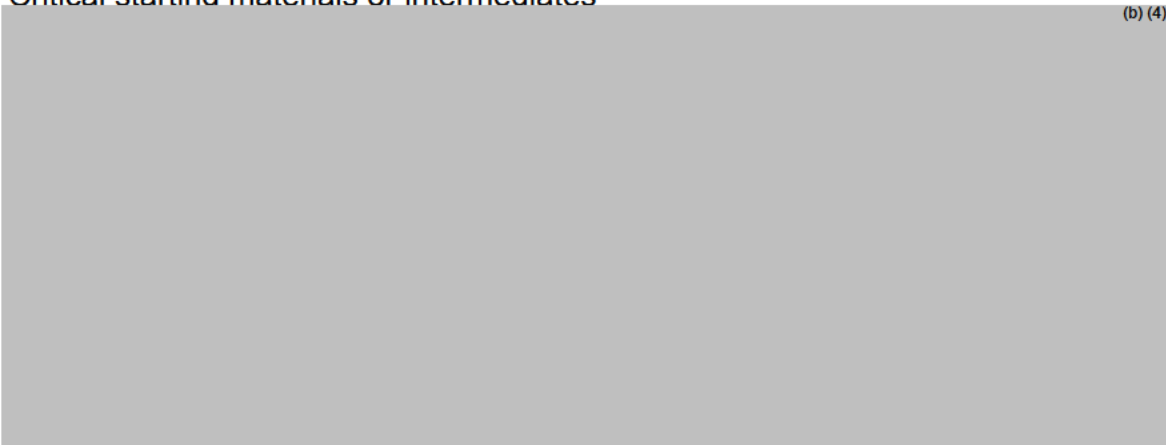
added to the samples and luminescence is measured using a luminescence plate reader. Potency is calculated using logarithmic response fitting-parallel line analysis with a minimum of five points in the linear range and is expressed as average relative potency.

d. Reference material(s)

The current RM was produced from DS manufactured using the clinical material manufacturing process. The RM is intended for use in both routine trastuzumab-dkst testing and qualification of new RM and is suitable for its intended purposes. The criteria used to evaluate the stability of the RM are acceptable. The applicant was requested to implement a two-tiered RM system consisting of a Primary RM (PRM) and a Working RM (WRM) as soon as possible. The procedures and criteria proposed for use in qualifying future RM are not sufficient and therefore were removed from the BLA.

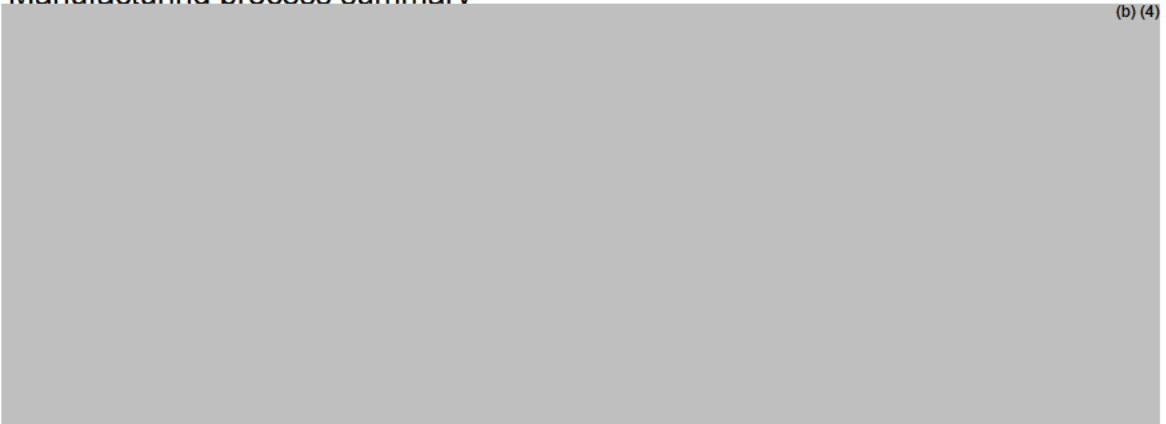
e. Critical starting materials or intermediates

(b) (4)



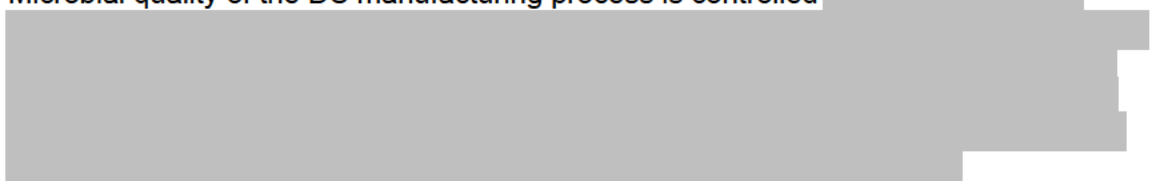
f. Manufacturing process summary

(b) (4)



Microbial quality of the DS manufacturing process is controlled

(b) (4)



The control strategies for DS and DP include control and monitoring of critical and non-critical operating process parameters, in-process testing for microbial control and assessment of other outputs that ensure product quality and allow for monitoring of performance attributes, and release and stability testing of DS and DP. Critical parameters selected for routine monitoring relate to (b) (4), assurance of acceptable levels of critical quality attributes (CQAs), including potency and strength, and assurance of correct formulation.

g. Container closure

The DS stored in (b) (4). The container closure system is suitable for trastuzumab-dkst, based on stability data and maintenance of closure integrity.

h. Dating period and storage conditions

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

C. Drug Product [Ogivri] Quality Summary

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

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (DP) (contaminant)	Safety (infection) and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination introduced throughout DP manufacturing process or due to failure of container closure integrity	(b) (4)	
Container Closure Integrity (sterility assurance)	Safety (sterility assurance)	Manufacturing failure or impact of storage conditions		N/A
Endotoxin (contaminant)	Safety and Purity	Contamination introduced throughout DP manufacturing process or due to failure of container closure integrity		N/A
Color and clarity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Lyophilized cake appearance	Safety and Efficacy (stability)	Manufacturing process		N/A
Moisture content	Efficacy (stability)	Manufacturing Process		N/A
Particulate Matter (visible and subvisible)	Safety/ Immunogenicity	Manufacturing process and container closure system		N/A



(b) (4)

(Product or Process Related Impurities)				
PEG 3350 concentration	Safety and Efficacy (control over degradation)	Manufacturing process		N/A
Deliverable Content (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		N/A

a. Potency and Strength

Ogivri is supplied at 420 mg/vial. Potency is defined as the percent activity relative to the current trastuzumab-dkst RM. The potency assays are the same as described in the DS section of this memo.

b. Summary of Product Design

Ogivri is supplied as a sterile, multi-dose, preservative-free lyophilized powder for IV infusion in a 50 mL vial. Ogivri is formulated in 322.6 mg D-sorbitol, 6.0 mg L-histidine, 9.4 mg L-histidine hydrochloride monohydrate, and 94.1 mg polyethylene glycol (PEG) 3350. Reconstitution with 20 mL diluent yields a solution containing 21 mg/mL trastuzumab-dkst at a pH of approximately 6. The deliverable amount is 420 mg. Ogivri is supplied with a 20 mL vial of bacteriostatic WFI (BWFI), USP. (b) (4). Ogivri reconstituted with BWFI can be stored for up to (b) (4) at (b) (4)°C.

c. List of Excipients

Excipients include L-histidine, L-histidine hydrochloride monohydrate, D-sorbitol, and PEG 3350. All excipients are compendial; the histidine hydrochloride monohydrate follows the requirements of Ph.Eur., because there is no USP monograph/chapter for this material.

d. Reference material(s)

The same reference material is used for DS and DP.

e. Manufacturing process summary

DP is manufactured at (b) (4). The DS is (b) (4). (b) (4). The vials are visually inspected, labeled, and packaged. The DP is stored at 2-8°C.

f. Container closure

The primary container closure system for Ogivri consists of a 50 mL (b) (4) glass vial that is closed with a 20 mm grey (b) (4) stopper and sealed with a 20 mm flip-off aluminum cap. The secondary packaging consists of a (b) (4) cardboard box.

The primary container closure system for BWFI is the same as that of Ogivri, with the exception of size (20 mL).

g. Dating period and storage conditions

The dating period for Ogivri will be 48 months when stored at 2-8°C, protected from light.

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

The expiry for the cartoned presentation will be based on the earliest expiry of either of the components included.

D. Analytical Similarity

The analytical similarity assessment was performed to demonstrate that Ogivri and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components, and to establish the analytical portion of the scientific bridges among Ogivri, US-Herceptin, and EU-Herceptin to justify the relevance of the comparative clinical and non-clinical data generated using EU-Herceptin. The similarity assessments were based on pairwise comparisons of the analytical data generated by the applicant or their contract laboratory using several lots of each product. We performed confirmatory statistical analyses of the data submitted, which included results from an assessment of up to 16 lots of Ogivri, 28 lots of US-Herceptin, and 38 lots of EU-Herceptin. All lots of each product were not included in every assessment; the number of lots analyzed in each assay was determined by the applicant based on the availability of test material at the time of analysis, orthogonal analytical techniques, variability of the analytical method, method qualification, and use of a common internal reference material.

The expiration dates of the US-Herceptin and EU-Herceptin lots included in the similarity assessment spanned approximately 6 years (2013 to 2019), and the Ogivri lots used for analysis were manufactured between 2011 and 2015.

The analytical similarity exercise included a comprehensive range of methods (listed in 4), which included orthogonal methods for the assessment of critical quality attributes. A number of assays were designed to specifically assess the potential mechanisms of action of trastuzumab, including Fc-mediated functions. All methods were validated or qualified prior to the time of testing and were demonstrated to be suitable for the intended use.

Table 4. Quality Attributes and Methods Used to Evaluate the Analytical Similarity of Ogivri, US-Herceptin and EU-Herceptin

Quality Attribute	Methods	Tier
Primary structure	• Peptide mass fingerprinting by liquid chromatography (LC) with electrospray (ESI) mass spectrometry (MS) detection	• Tier 3
	• Intact molecular mass (LC-ESI-MS)	• Tier 3
	• Reduced molecular mass (LC-ESI-MS)	• Tier 3
Protein content	• Concentration [ultraviolet (UV) spectroscopy at 280 nm]	• Tier 2
Higher order structure	• Near and far UV circular dichroism (CD)	• Tier 3/2
	• Fourier transform infrared spectroscopy (FTIR)	• Tier 3
	• Intrinsic fluorescence (IF)	• Tier 3
	• LC-ESI-MS (disulfide bond characterization)	• Tier 3
	• Differential scanning calorimetry (DSC)	• Tier 3
	• Ellman's reagent (free cysteines)	• Tier 3
Size Variants/Aggregates	• Size exclusion high performance liquid chromatography (SEC-HPLC) with UV detection	• Tier 2
	• SEC with multi-angle light scattering (MALS)	• Tier 3
	• Analytical ultracentrifugation sedimentation velocity (AUC)	• Tier 3
	• Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS, Reduced and Non-Reduced)	• Tier 2
Charge and Hydrophobic variants	• Capillary isoelectric focusing (cIEF)	• Tier 3
	• Cation exchange HPLC (CEX-HPLC)	• Tier 2
	• Hydrophobic interaction chromatography (HIC-HPLC)	• Tier 3
	• LC-ESI-MS (oxidation)	• Tier 3
Glycosylation	• Normal phase (NP)-HPLC (glycan mapping)	• Tier 2
	• Reverse phase (RP)-HPLC (afucosylation and sialic acid)	• Tier 2
	• CE-SDS reduced (Non-glycosylated heavy chain)	• Tier 2
	• Boronate affinity chromatography (glycation)	• Tier 3
Potency	• HER2 binding assay by flow cytometry	• Tier 1
	• Inhibition of proliferation bioassay	• Tier 1
	• Antibody-dependent cellular cytotoxicity (ADCC) bioassay (PBMC as effector cells)	• Tier 1
Fc-receptor binding and function	• FcγRIIIa V type binding affinity (b) (4)	• Tier 2
	• FcγRIIIb binding affinity (b) (4)	• Tier 3
	• FcγRIIa binding affinity	• Tier 3
	• FcγRIIb binding affinity	• Tier 3
	• FcγRIa binding affinity (b) (4)	• Tier 3
	• FcRn binding affinity (b) (4)	• Tier 2
	• Cellular dependent cytotoxicity (CDC) bioassay	• Tier 3
	• C1q binding assay (ELISA)	• Tier 3

Primary Structure

To support a demonstration that Ogivri is highly similar to US-Herceptin, it is expected that the expression construct for the proposed biosimilar product encodes the same primary amino acid sequence as US-Herceptin. To achieve this goal, expression constructs were designed to encode a protein sequence that matches US-Herceptin. This can be confirmed at the protein level by methods including a variety of MS approaches, as described below.

Peptide mapping

The primary structure assessments of Ogivri, US-Herceptin, and EU-Herceptin, performed by peptide mapping with two different enzymes, demonstrated that the chromatographic profile (peptide map) and primary amino acid sequence of Ogivri match those of US-Herceptin and EU-Herceptin. No additional peptides or missing peptides were detected among the three products.

Further primary structure analysis

Additional assessments of primary structure, including molecular mass determination for the intact antibody and an evaluation under reducing conditions where the heavy chains (HC) and light chains (LC) of each molecule were assessed separately, were conducted for each product. The data show similar masses for Ogivri, US-Herceptin, and EU-Herceptin under reducing and non-reducing conditions, and the measured masses correlated with the expected molecular masses.

Trastuzumab has 16 disulfide bonds, including 12 intra-chain and 4 inter-chain linkages. Analysis by non-reduced peptide mapping using RP-HPLC-MS showed the presence of the same intra-chain and inter-chain disulfide bonds in all three products. The expected HC to LC inter-chain disulfide bond was not identified in any of the products using this method; however, an additional analysis was used to identify this bond, and free cysteine analysis identified no free cysteines in any of the products, indicating that the expected disulfide bonds are fully formed.

Protein Content

US-Herceptin is marketed in a multi-dose vial containing 420 mg of drug product with a protein concentration of 21 mg/ml upon reconstitution. The EU-Herceptin 150 mg presentation also has a reconstituted protein concentration of 21 mg/ml. The data confirm that the reconstituted protein concentrations in the Ogivri vials are similar to those of the US-Herceptin and EU-Herceptin vials. The Ogivri manufacturing process was designed to match the protein content of US-Herceptin, within reasonable manufacturing tolerances. The recoverable protein amounts (420 mg) for the Ogivri and US-Herceptin vials are similar.

Higher Order Structure

The secondary and tertiary structures of the three products were evaluated using far and near UV CD, FTIR, DSC and IF. Proper folding is critical for the effective function and serum half-life of proteins.

Information regarding secondary structure (α -helix, β -sheet and random coil structures) was provided by the far UV CD spectroscopy and FTIR results, and information on tertiary structure was provided by the near UV CD and IF results. All four methods yielded overlapping spectra among the Ogivri, US-Herceptin, and EU-Herceptin lots evaluated.

DSC was used to measure the melting temperatures of the protein subunits. Quantitative analysis and representative thermograms demonstrate structural similarity among the three products.

Aggregates and Low Molecular Weight Species

Biopharmaceuticals typically contain low levels of protein aggregates at the time of release, and the levels often increase with the age of the product. They are measured for lot release and as part of long term stability studies, and are controlled by release requirements and expiry periods. Small amounts of aggregation are present in Ogivri, US-Herceptin, and EU-Herceptin. Aggregation is typically detected and quantified by SEC-HPLC. The average level of aggregates in US-Herceptin as quantified by the applicant's SEC-HPLC assay was 0.47%, while the level in Ogivri was 0.30% and the level in EU-Herceptin was 0.46%; AUC data support these results. Ogivri has marginally lower levels of aggregates compared to US-Herceptin and EU-Herceptin, but the results were within a quality range established based on the US-Herceptin data (mean $\pm$ 3sd) or EU-Herceptin data (for the comparison of Ogivri to EU-Herceptin). Based on stability data, the difference in the average levels of aggregates is likely to be due to differences in the ages of the lots at the time of analysis. From a quality standpoint, aggregation may have implications for product immunogenicity or potency. Here, the aggregation levels observed and the identified differences do not preclude a demonstration that the products are highly similar and are not expected to have any clinical impact.

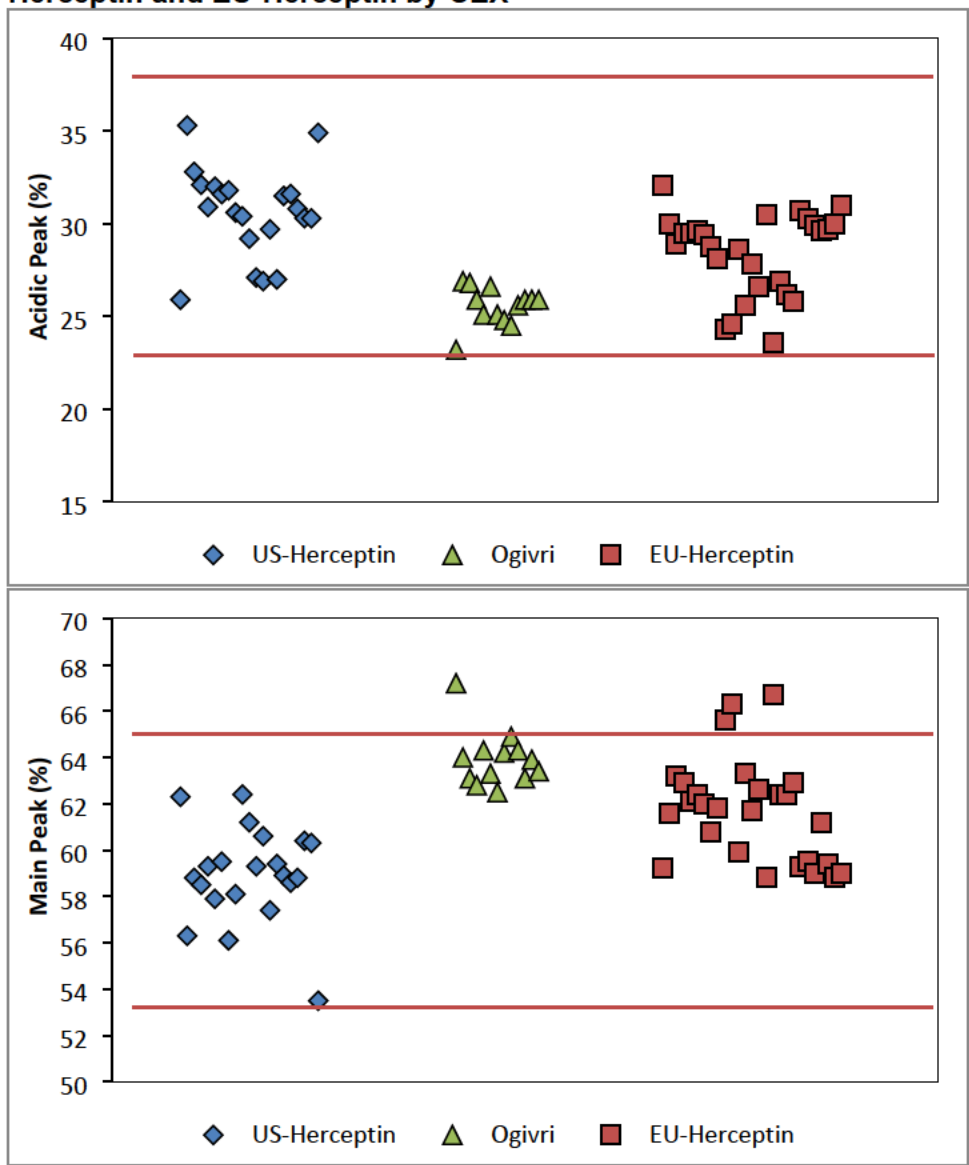
Low molecular weight species (LMWS), such as free HC or LC, incomplete combinations of HC and LC, and proteolyzed species, were evaluated using non-reduced and reduced CE-SDS. Ogivri total fragment and monomer levels were within the quality ranges established (mean $\pm$ 3sd); however, there were minor differences with respect to individual LMWS. Specifically, for LC, Fab/HC, and 2H1L variants, 8-17% of the Ogivri lots (1-2 lots) were outside the quality range established based on the US-Herceptin data. With the exception of the LC, these results met the expectation that 90% of the individual lots are within the quality range; however, for the LC, one of the US-Herceptin lots was also outside its established quality range. The levels of each of these variants were very low (<1% for LC and Fab/HC; <2% for 2H1L), and the differences do not preclude a demonstration that the products are highly similar and are not expected to have clinical impact.

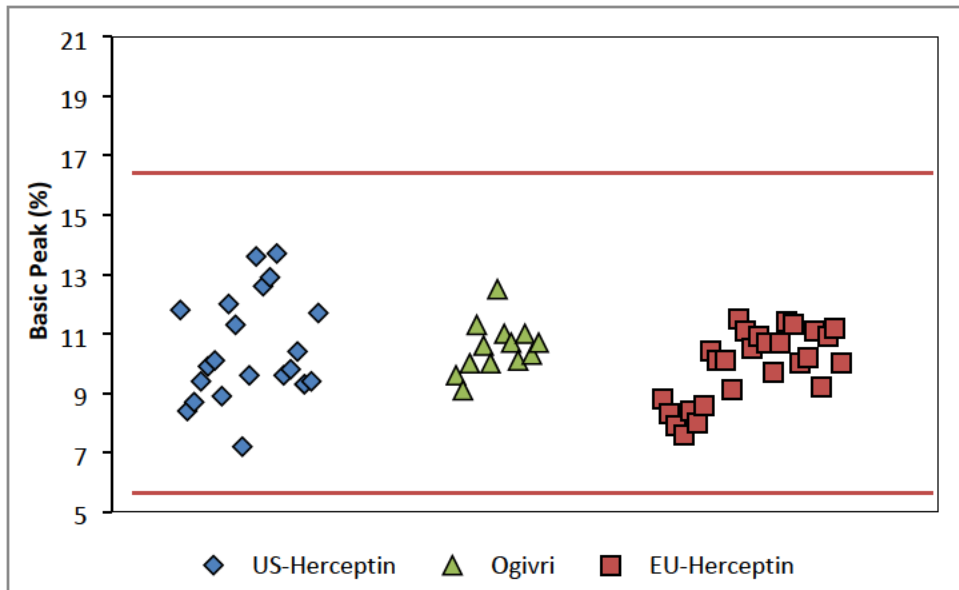
Charge Variants

Charge heterogeneity is commonly observed for monoclonal antibodies. The heterogeneity is derived from product variants that typically include deamidation, glycation, oxidation, heterogeneity of the cleavage of the C-terminal chain, and sialylation. These variants result in a complex charge profile. In cation exchange chromatography (CEX) and capillary isoelectric focusing (cIEF) assays, the charge profiles for Ogivri, US-Herceptin, and EU-Herceptin are resolved into three distinct

groups: acidic peaks, basic peaks and the main peak. Although the results for most Ogivri lots were within the quality range criteria calculated (mean $\pm$ 3sd), some differences in the levels of acidic peak group and main peak were observed among the three products. Specifically, Ogivri generally had lower levels of acidic peaks and higher levels of main peak with respect to US-Herceptin and EU-Herceptin (Figure 1). No significant differences were observed in the levels of basic peaks among the three products. The quality range criteria developed by the applicant using US-Herceptin results are depicted by the red lines in Figure 1 and other figures presented below. cIEF analyses also revealed small differences in charge variants.

Figure 1. Comparison of Charge Variant Profile Peak Levels for Ogivri, US-Herceptin and EU-Herceptin by CEX





Source: FDA analysis of the 351(k) BLA submission

To evaluate the nature of the observed differences, the applicant performed characterization studies. These studies suggest that the difference in the levels of the acidic and main peaks may be due, in part, to differences in deamidation at LC asparagine 30 (Asn30), which is in the complementarity-determining region (CDR). All three molecules exhibited Asn30 deamidation; however, in fractions highly enriched in acidic variants, the cumulative amount of Asn30 deamidation was greater in US-Herceptin and EU-Herceptin lots than in Ogivri. The magnitude of the acidic variant differences driven by Asn30 deamidation is not expected to impact immunogenicity or PK.

A small decrease in the levels of basic peaks and increase in the level of main peak in Ogivri lots relative to US-Herceptin and EU-Herceptin may be related to a lower level of C-terminal lysine in Ogivri. Differences in C-terminal lysine levels for products administered via intravenous infusion are considered to not have clinical impact, because this amino acid is expected to be cleaved shortly after infusion into patients.

In addition to the minor differences in levels of charge variants, two additional peaks were detected in the Ogivri IEC chromatograms; one peak is in the acidic region, and one peak is in the basic region. The characterization data provided indicate that the basic variant is related to oxidation at methionine 255 (Met 255) and that the acidic variant is related to Asn30 deamidation. These peaks are not well resolved but appear to be present at extremely low levels. Given the amounts and nature of these variants (i.e., the identified modifications are not different than those found in US-Herceptin) they are not expected to have clinical impact and do not preclude a determination of highly similar.

Additionally, product variants were evaluated by separation of the molecules using HIC. The HIC analysis showed minor differences among the three products; these differences were similar in magnitude to those identified using IEX-HPLC and cIEF and likely result from the same variants. Oxidation at M255, located in the Fc region of the HC, and

glycation were also evaluated, and the data show that Ogivri lots were within the range of variability observed in the US-Herceptin and EU-Herceptin lots.

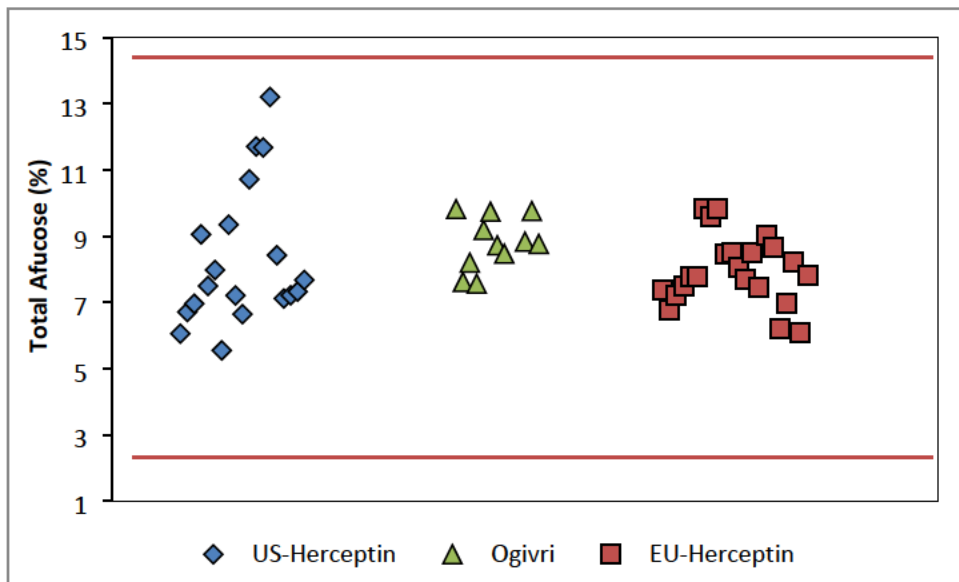
Glycosylation

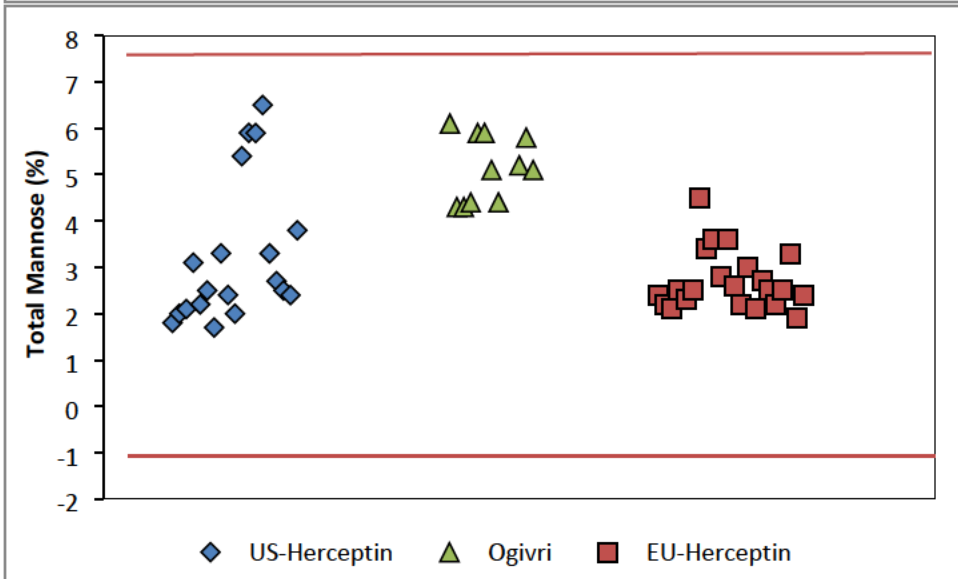
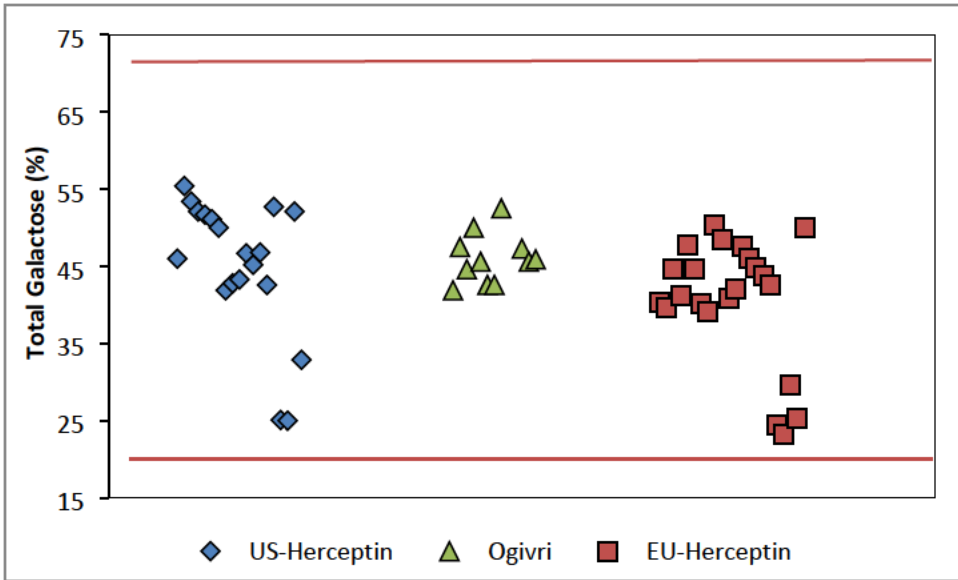
Trastuzumab is a glycoprotein containing one N-glycan in the Fc region of each HC of the molecule. Antibody glycosylation is typically heterogeneous and is variable among antibody products and, to some extent, among lots of a specific product. NP-HPLC, RP-HPLC (with and without MS) and CE-SDS reduced were used to determine the content of various glycoforms. Altogether, 13 N-glycan groups were identified; the most abundant forms were G0F and G1F.

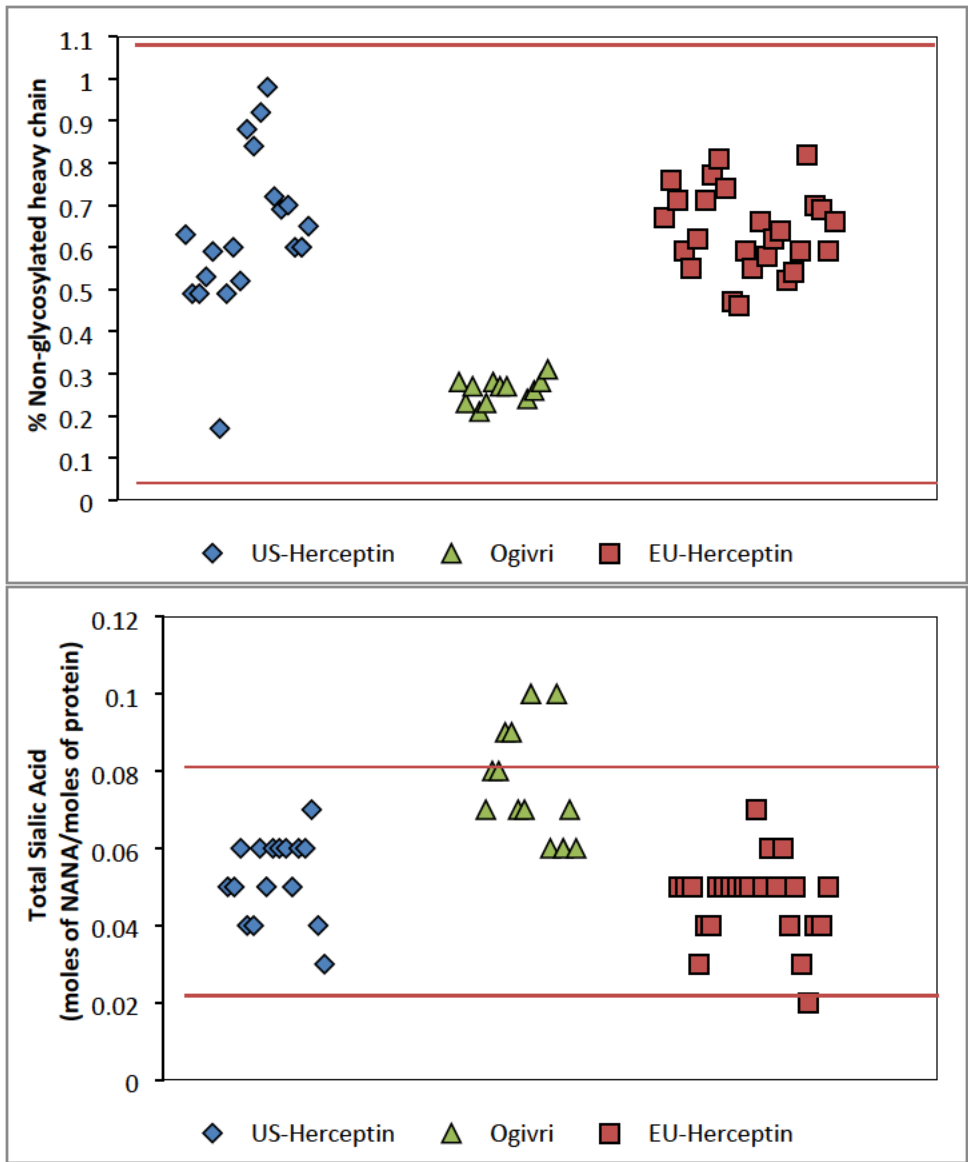
Glycoforms containing fucose at the base of the biantennary structure can influence the Fc three-dimensional structure and lower the binding affinity of the molecule to Fc receptors such as FcγRIIIa. Other differences in glycosylation, such as in levels of high mannose and sialylation, can influence the PK profile of the molecule.

Differences were observed in the amount of various glycoforms present among the three products as shown in Figure 2 below.

Figure 2. Comparison of Glycan Profile for Ogivri, US-Herceptin and EU-Herceptin







Source: FDA analysis of the 351(k) BLA submission

The applicant evaluated glycosylation using NP-HPLC and utilized an RP-HPLC-MS method as an orthogonal method for evaluating afucosylation. Total levels of afucosylated isoforms were determined from Ogivri, US-Herceptin and EU-Herceptin lots assessed using NP-HPLC by calculating the sum of glycan structures lacking core fucose, including high mannose glycans (Man 5 and Man 6). The NP-HPLC analysis shows similar afucosylation levels among the three products; the RP-HPLC-MS data support these results.

High mannose and sialylated glycan structures can alter the PK of a molecule through binding to cell surface mannose binding proteins and through reduced FcRn binding, respectively. Differences in the levels of high mannose forms (Man 5 and Man 6) and sialic acid were noted among the products. Specifically, 31% of Ogivri lots were outside the sialic acid quality range criteria calculated using the US-Herceptin data (mean $\pm$ 3sd), and while the lots were within the quality range criteria, Ogivri generally had higher levels of mannose compared to the majority of the US-Herceptin and EU-Herceptin lots.

Although there are differences in the sialic acid levels, the levels are extremely low among all three products (no more than 0.10 mol/mol). Ogivri lots with minor differences in glycosylation with respect to the US-Herceptin lots were included among those used in clinical studies. Residual uncertainty about biosimilarity that resulted from the differences in high mannose and sialylated glycans is adequately addressed by data that showed no impact of these differences on PK. These differences do not preclude a demonstration that the products are highly similar.

The lack of glycosylation in the Fc region of the HC of an antibody has been correlated with loss of effector function, increased aggregation, and structural changes. Ogivri had lower levels of NG-HC compared to US-Herceptin and EU-Herceptin. Lower NG-HC is not a concern from the safety perspective, because a lack of glycosylation correlates with a reduction in Fc receptor binding and effector function. Because effector function is a primary mechanism of action of trastuzumab, the lower levels of NG-HC in Ogivri could potentially impact product efficacy. However, the overall levels of NG-HC were very low (<1%) among the three products, and given the ADCC activity and FcγRIIIa binding results discussed below, these differences do not preclude a determination that Ogivri and US-Herceptin are highly similar.

Biological Activity

A number of bioassays were designed and qualified to evaluate potential trastuzumab functions including binding of HER2, inhibition of proliferation, and ADCC activity. The data are reported relative to the applicant's in-house Ogivri reference material.

HER2 binding

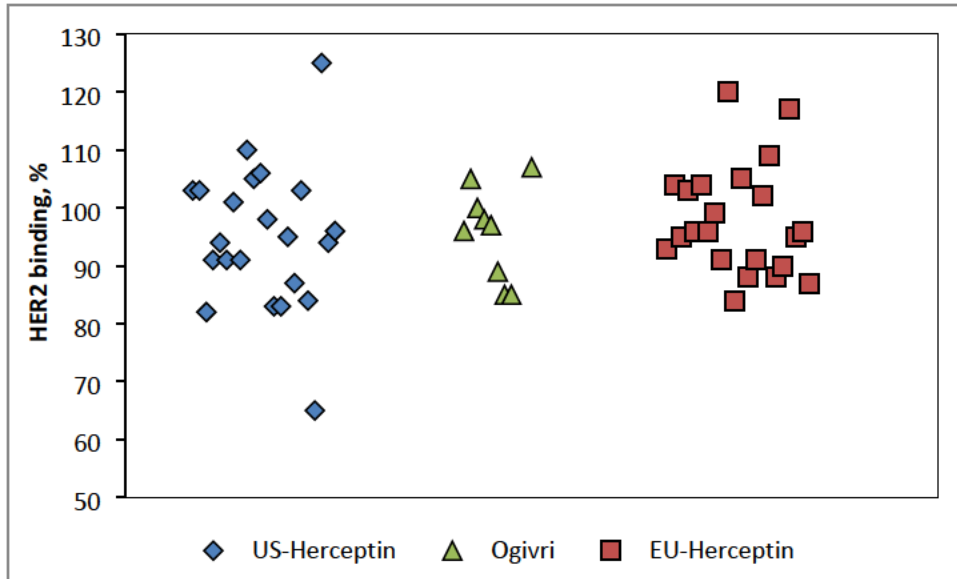
A comparison of the relative HER2 binding of Ogivri, US-Herceptin, and EU-Herceptin was carried out with 9 to 22 lots of each product (Table 5 and Figure 3). Because of the criticality of the HER2 binding attribute, these data were subjected to a statistical analysis using equivalence testing. The HER2 binding activity of Ogivri would be considered statistically equivalent to the HER2 binding activity of US-Herceptin if the 90% confidence interval (CI) of the mean difference in HER2 binding between Ogivri and US-Herceptin is entirely within the equivalence acceptance criterion calculated using the applicant's US-Herceptin HER2 binding data. Similarly, the binding activity of Ogivri was compared to an equivalence acceptance criterion calculated using the EU-Herceptin data, and the binding activity of EU-Herceptin was compared to an equivalence acceptance criterion calculated using the US-Herceptin data. Equivalence testing results for the HER2 binding data for Ogivri, US-Herceptin, and EU-Herceptin are shown in Table 6.

Table 5. Descriptive Statistics for the HER2 Binding Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
Ogivri	9	96	8.0	85	107
US-Herceptin	22	95	12.0	65	125
EU-Herceptin	22	98	9.0	84	120

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 3. Comparative Potency of Ogivri, US-Herceptin and EU-Herceptin- Binding to Human HER2



Source: FDA analysis of data from the Applicant 351(k) BLA submission

Table 6. Equivalence Testing Results for the HER2 Binding

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
Ogivri vs. US	(9, 22)	0.008	(-0.065, 0.081)	(-0.184, 0.184)	Yes
Ogivri vs. EU	(9, 22)	-0.021	(-0.084, 0.043)	(-0.141, 0.141)	Yes
EU vs. US	(22, 22)	0.029	(-0.027, 0.084)	(-0.184, 0.184)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission

The statistical equivalence analyses shown in Table 6 support the conclusion that Ogivri is highly similar to US-Herceptin. Further, these analyses support the analytical component of the scientific bridges among US-Herceptin, EU-Herceptin, and Ogivri to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

Inhibition of proliferation

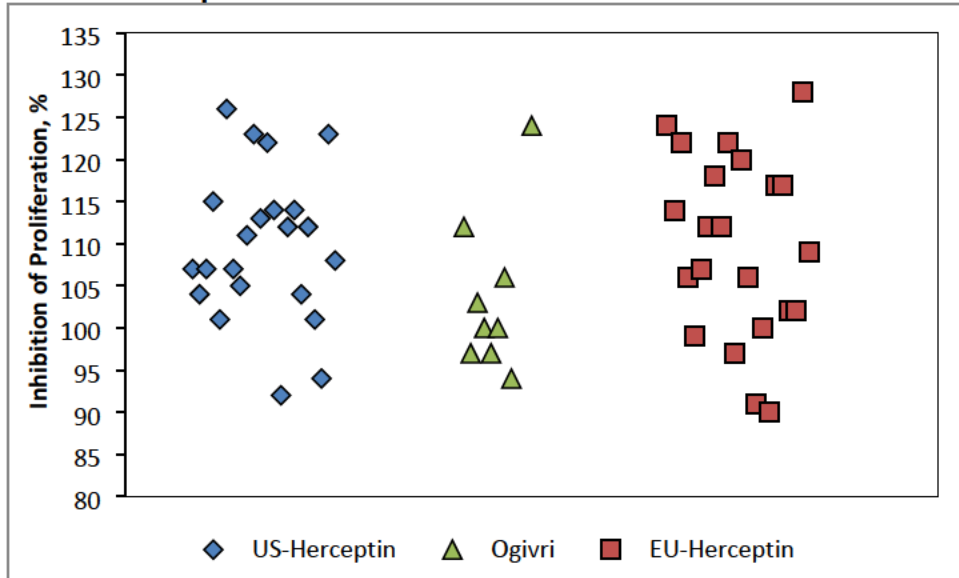
A comparison of the relative potency of Ogivri, US-Herceptin, and EU-Herceptin was carried out with 9 to 22 lots of each product (Table 7 and Figure 4). Because of the criticality of this attribute, these data were subjected to a statistical analysis using equivalence testing. The Ogivri capacity for inhibition of proliferation (potency) would be considered statistically equivalent to the potency of US-Herceptin if the 90% CI of the mean difference in potency between Ogivri and US-Herceptin is entirely within the equivalence acceptance criterion calculated from the applicant’s US-Herceptin inhibition of proliferation data. Similar analyses were performed for the other pairwise comparisons. Equivalence testing results for the Ogivri, US-Herceptin, and EU-Herceptin data are shown in Table 8.

Table 7. Descriptive Statistics for the Inhibition of Proliferation Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
Ogivri	9	104	9.0	94	124
US-Herceptin	22	110	9.0	92	126
EU-Herceptin	22	110	11.0	90	128

Source: FDA analysis of data from the 351(k) BLA submission

Figure 4. Comparative Potency (Inhibition of Proliferation) of Ogivri, US-Herceptin and EU-Herceptin



Source: FDA analysis of data from the 351(k) BLA submission

Table 8. Equivalence Testing Results for the Inhibition of Proliferation

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
Ogivri vs. US	(9, 22)*	-0.061	(-0.130, 0.007)	(-0.134, 0.134)	Yes
Ogivri vs. EU	(9, 22)*	-0.061	(-0.134, 0.012)	(-0.161, 0.161)	Yes
EU vs. US	(22, 22)	0.000	(-0.050, 0.050)	(-0.134, 0.134)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission

* The 90% CI is adjusted for the sample size imbalance.

The statistical equivalence analyses shown in Table 8 support the conclusion that Ogivri is highly similar to US-Herceptin. Further, these analyses support the analytical component of the scientific bridges among US-Herceptin, EU-Herceptin, and Ogivri to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

ADCC

A comparison of the relative ADCC activity of Ogivri, US-Herceptin, and EU-Herceptin was carried out with 13 to 26 lots of each product (Table 9 and Figure 5). Because of the criticality of this attribute, these data were subjected to a statistical analysis using equivalence testing. The ADCC activity of Ogivri would be considered statistically equivalent to the ADCC activity of US-Herceptin if the 90% CI of the mean difference in

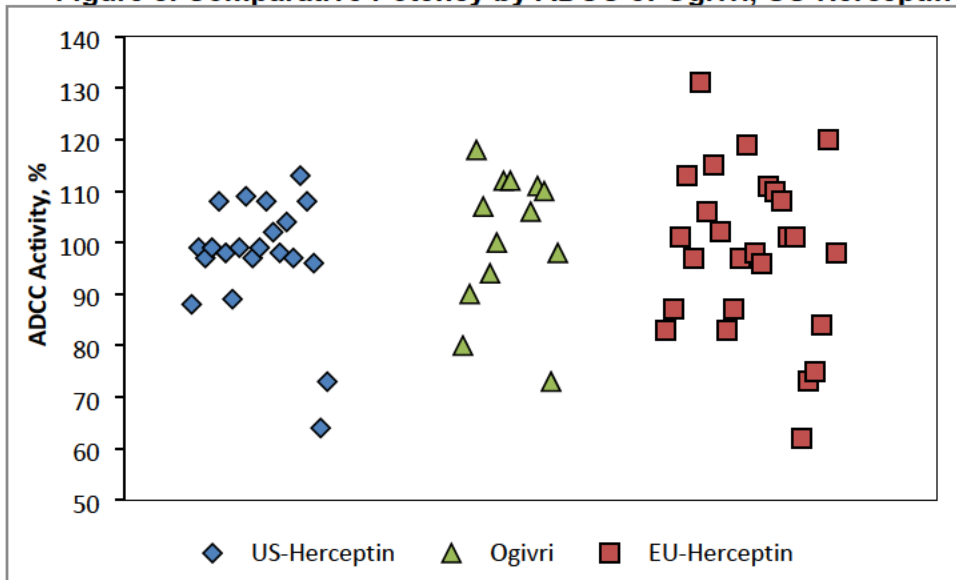
activity between Ogivri and US-Herceptin is entirely within the equivalence acceptance criterion calculated from the applicant’s US-Herceptin data. Similar analyses were performed for the other pairwise comparisons. Equivalence testing results for the Ogivri, US-Herceptin, and EU-Herceptin ADCC data are shown in Table 10.

Table 9. Descriptive Statistics for the ADCC Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
Ogivri	13	101	13.0	73	118
US-Herceptin	21	97	12.0	64	113
EU-Herceptin	26	98	16.0	73	131

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 5. Comparative Potency by ADCC of Ogivri, US-Herceptin and EU-Herceptin



Source: FDA analysis of data from the Applicant 351(k) BLA submission

Table 10. Equivalence Testing Results for ADCC activity

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
Ogivri vs. US	(13, 21)*	0.035	(-0.043, 0.113)	(-0.173, 0.173)	Yes
Ogivri vs. EU	(13, 26)*	0.025	(-0.012, 0.090)	(-0.240, 0.240)	Yes
EU vs. US	(26, 21)	0.010	(-0.058, 0.078)	(-0.173, 0.173)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission

* The 90% CI is adjusted for the sample size imbalance.

The statistical equivalence analyses shown in Table 10 support the conclusion that Ogivri is highly similar to US-Herceptin. Further, these analyses support the analytical component of the scientific bridges among US-Herceptin, EU-Herceptin, and Ogivri to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

Fc Function

Complement dependent cytotoxicity (CDC) activity

The Fc region of an antibody HC contains amino acid residues that can interact with complement C1q to mediate CDC. In CDC, the complement system is activated when C1q interacts with antibodies bound to cell surface targets, which initiates a biological cascade that ultimately results in pore formation in the target cell membrane. CDC is not currently understood to be a mechanism of action of trastuzumab; however, a comparison of C1q binding and CDC activity was performed based on the capacity of IgG1 molecules to perform this function. The C1q binding activity of Ogivri, US-Herceptin, and EU-Herceptin was evaluated using an enzyme-linked immunosorbent assay (ELISA). The relative binding activities were similar among the three products. CDC activity was evaluated using an in vitro assay in which SKBR3 cells were incubated with increasing concentrations of Ogivri, US-Herceptin, or EU-Herceptin in the presence or absence of human plasma as a source of complement. CDC activity was measured using a fluorescent marker sensitive to the presence of cell death components released upon cell lysis. No difference in CDC activity of Ogivri, US-Herceptin and EU-Herceptin was observed.

Binding to Fc Receptors

The Fc receptors, FcγRI, FcγRII, FcγRIII and FcRn, are diverse in structure and cell type expression. The predominant Fc receptor type on NK cells is FcγRIII (a or b forms), while other leukocytes express a broader range of Fc receptors. FcγRI and FcγRII isoforms may contribute to effector function, depending on the effector cell type at the site of disease. The neonatal Fc receptor, FcRn, plays an important role in IgG homeostasis, by binding the Fc region in a pH dependent manner and protecting the molecule from lysosomal degradation, thus prolonging the half-life of the molecule. Therefore, binding to both Fcγ receptors and FcRn was assessed using surface plasmon resonance (SPR)-based assays. Small differences were noted in the binding kinetics of Ogivri, US-Herceptin, and EU-Herceptin to FcγRIa, FcγRIIa, FcγRIIb/c, FcγRIIIa V158, FcγRIIIb and FcRn. SPR-based assays generally have relatively high amounts of variability. Residual uncertainty about biosimilarity that resulted from the differences in binding kinetics is adequately addressed by data that showed no impact of these differences on ADCC and PK. The differences in Fc receptor binding among Ogivri, US-Herceptin, and EU-Herceptin were determined not to preclude a demonstration that Ogivri and US-Herceptin are highly similar.

Comparative Stability Studies

The applicant evaluated the stability of Ogivri, US-Herceptin, and EU-Herceptin in several studies, including evaluations of thermal stability at 25°C for 6 months and at 40°C for 3 months and forced degradation studies using exposure to light, low and high pH, and oxidizing conditions. The products were evaluated both as a lyophilized powder and following reconstitution. Accumulation of high and low molecular weight species (SEC-HPLC and CE-SDS reducing and non-reducing), changes in charge variants (CEX-HPLC), loss of function (HER2 binding and/or FcγRIIIa binding), conformational changes (CD and IF), and protein concentration (UV detection) were evaluated. The stability patterns of the three products were similar in all studies.

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2-8°C.
- Store in original carton until time of use.
- Protect from light until use.
- Do not freeze.



G. Establishment Information

OVERALL RECOMMENDATION:

DRUG SUBSTANCE

Site Name	Address	FEI/DUNS Number	Responsibility	Final Recommendation
(b) (4)				Approve
				Approve

DRUG PRODUCT

Site Name	Address	FEI Number	Responsibility	Final Recommendation
(b) (4)				Approve

H. Facilities

This application is recommended as approve from a facility review perspective.

For the proposed drug substance and drug product manufacturing site, two inspections were recently conducted for [REDACTED] (b) (4); a PLI from [REDACTED] (b) (4) and a surveillance inspection from [REDACTED] (b) (4)

Observations from both inspections were reviewed to consider potential impact to the proposed operations for Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) drug product manufacturing. Corrective actions from the PLI conducted from [REDACTED] (b) (4) were completed and deemed adequate.

Corrective actions from the surveillance inspection conducted from [REDACTED] (b) (4) were completed and deemed adequate. In response to the observations, the firm proposed 59 CAPAs, including installation [REDACTED] (b) (4)

Additional updates were received from the firm on [REDACTED] (b) (4) stated that 58 of the 59 CAPAs are complete.

The remaining open CAPA is not related to processing this product. The [REDACTED] (b) (4) reports submitted summarizing the three media fills completed, adequately support [REDACTED] (b) (4) from a GMP facility review standpoint. Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) is proposed [REDACTED] (b) (4). Based on the additional information received from the firm, BLA 761074 for manufacture of Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) is recommended for approval.

I. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved: At-scale validation of [REDACTED] (b) (4) DS annual stability protocol, and DS stability protocol for extension of expiry
- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None

b. Drug Product

- i. Protocols approved: DP and BWFI annual stability protocols and BWFI stability protocol for extension of expiry
- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: [REDACTED] (b) (5)



Kathleen
Clouse Strebel

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Reyes
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Zihao Peter
Qiu

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BLA STN 761074

OGIVRI (trastuzumab-dkst)

Mylan GmbH

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Division of Biotechnology Review and Research I
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. **BLA#:** STN 761074
2. **REVIEW DATE:** October 26, 2017
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Suparna Wedman, Jennifer Gao, and Laleh Amiri Kordestani (Team Leader [TL] and CDTL)
Pharm/Tox: Haw-Jyh Chiu and Todd Palmby (TL)
Product Quality Team: Kristen Nickens and Sarah Kennett (ATL)
Immunogenicity: Brian Janelsins and Rachel Novak (TL)
Microbiology and Facilities: Lakshmi Narasimhan, Maria Candauchacon, Patricia Hughes (TL), Michael Shanks, Peter Qui (TL)
Clinical Pharmacology: Brian Furmanski and Sarah Schrieber (TL)
Statistics: Li Xing, Meiyu Shen, Yi Tsong (TL)
OBP Labeling: Vicky Borders-Hemphill
ORPO RBPM: Keith Olin
RPM: Charlene Wheeler
4. **MAJOR GRMP DEADLINES**
Filing Meeting: December 14, 2016
Mid-Cycle Meeting: May 1, 2017
Wrap-Up Meeting: August 2, 2017
Primary Review Due: October 27, 2017
CDTL Memo Due: November 4, 2017
BSUFA Action Date: December 3, 2017
5. **COMMUNICATIONS WITH APPLICANT AND OND:**

Communication/Document	Date
Information Request #1	December 16, 2016
Filing Letter	December 30, 2016
Information Request #2	January 27, 2017
Information Request #3	February 16, 2017
Information Request #4	March 27, 2017
Information Request #5	May 5, 2017
Information Request #6	May 10, 2017
Information Request #7	June 2, 2017
Information Request #8	June 8, 2017
Information Request #9	July 12, 2017
Information Request #10	July 21, 2017
Information Request #11	August 17, 2017
Teleconference	September 7, 2017

Information Request #12	October 20, 2017

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
761074/0000	November 3, 2016	Yes
761074/0006	December 19, 2016	Yes
761074/0008	December 21, 2016	Yes
761074/0010	January 6, 2017	Yes
761074/0013	January 13, 2017	Yes
761074/0017	February 10, 2017	Yes
761074/0018	February 21, 2017	Yes
761074/0028	May 12, 2017	Yes
761074/0030	May 16, 2017	Yes
761074/0036	June 20, 2017	Yes
761074/0037	June 23, 2017	Yes
761074/0041	June 26, 2017	Yes
761074/0044	July 28, 2017	Yes
761074/0045	July 31, 2017	Yes
761074/0048	September 20, 2017	Yes
761074/0049	October 4, 2017	Yes
761074/0050	October 23, 2017	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Ogivri
- b. Trade Name: Ogivri
- c. Non-Proprietary/USAN: trastuzumab-dkst
- d. CAS name: 180288-69-1
- e. Common name: MYL-1401O
- f. INN Name: trastuzumab-dkst
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMANIZED (IGG1k) ANTI P04626 (HER2_HUMAN) [MYL-1401O]
- i. Other Names: Bmab-200, Hercules

8. **PHARMACOLOGICAL CATEGORY:** HER2/neu receptor antagonist

9. **DOSAGE FORM:** for injection

10. **STRENGTH/POTENCY:** 420 mg per vial

11. **ROUTE OF ADMINISTRATION:** Intravenous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

(b) (4)	Yes	(b) (4) Adequate information provided in the BLA for its intended use
	Yes	(b) (4) Adequate information provided in the BLA for its intended use
	Yes	(b) (4) Adequate information provided in the BLA for its intended use
	Yes	(b) (4) Adequate information provided in the BLA for its intended use
	Yes	(b) (4) specific information evaluated as part of BLA review
	Yes	(b) (4) Adequate information provided in the BLA for its intended use
	Yes	(b) (4) Adequate information provided in the BLA for its intended use

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of (b) (4) for the drug substance, drug product and analytical similarity data was conducted from (b) (4) by Reyes Candau-Chacon (Lead Inspector), Lakshmi Narasimhan (DMA), Michael Shanks (DIA), Sarah Kennett (OBP), and Kristen Nickens (OBP). An eight-item Form FDA 483 issued to Mylan at the end of the inspection included the following: (b) (4)

(b) (4). In addition, 17 recommendations were conveyed to the firm at the end of the inspection. Following the response provided by the applicant, the inspection outcome was VAI with a recommendation to withhold based on incomplete corrective and preventative actions.

Following this PLI, a surveillance inspection was conducted by FDA Office of Regulatory Affairs (ORA) from [REDACTED] ^{(b) (4)}. The current status is VAI.

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

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

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

15. PRECEDENTS

None

17. ADMINISTRATIVE

Signature Block

Discipline	Reviewer	Branch/Division	Signature
Drug substance, drug product, and analytical similarity	Kristen Nickens	Division of Biotechnology Review and Research I	See Panorama
Immunogenicity	Brian Janelsins	Division of Biotechnology Review and Research I	See Panorama
Immunogenicity TL	Rachel Novak	Division of Biotechnology Review and Research I	See Panorama
Division Director	Kathleen Clouse	Division of Biotechnology Review and Research I	See Panorama

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I recommend approval of STN 761074 for Ogivri (trastuzumab-dkst) manufactured by Mylan GmbH. The data submitted in this application support the conclusion that the manufacture of Ogivri is well controlled and consistently leads to a product with the appropriate potency and purity.

II. List Of Deficiencies To Be Communicated – N/A

III. List Of Post-Marketing Commitments/Requirement:

The following is a draft post-marketing commitment.

- a. Perform a method validation study to confirm the suitability of the FcγRIIIa-V₁₅₈ surface plasmon resonance (SPR) binding assay for use as a potency assay for drug substance and drug product lot release and stability testing. The final study results will be submitted to the BLA.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Mylan requested categorical exclusion from the environmental assessment requirement under 21 CFR 25.15 based on the consideration that MYL-1401O will not increase the use of the active moiety, so the environmental impact in terms of use and disposal will not be changed by this product 21 CFR 25.31(a).

While approval of this application may increase the use of the active moiety, a claim of categorical exclusion is acceptable based on 21 CFR 25.31(c).

V. Primary Container Labeling Review

The OBP review of the DP labeling was performed under separate cover by Vicky Borders-Hemphill (see review in Panorama).

VI. Review of Common Technical Document-Quality Module 3.2

The review of Module 3.2 is provided below.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assay validation is included following the DP review below.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

MYL-1401O is a proposed biosimilar to US-licensed Herceptin (trastuzumab) directed against the human epidermal growth factor receptor 2 (HER2). MYL-1401O is a humanized recombinant IgG1 monoclonal antibody of the kappa isotype consisting of two identical heavy chains (HCs), which are glycosylated at asparagine (Asn) residue 300, and two identical light chains (LCs).

Note: There were a substantial number of errors in the data and information presented in the original BLA submission. Where these errors impacted the review of the application or the manufacturing and controls for future lots of MYL-1401O, Mylan was requested to make corrections to the BLA. In the majority of instances, this is not discussed in the review, and the final data or information are presented below.

Tables and Figures are copied directly from the application, unless otherwise noted.

3.2.S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

- International Nonproprietary name (INN): trastuzumab-dkst
- United States Adopted Name (USAN): trastuzumab-dkst
- Chemical Abstracts Service (CAS) registry Number: 180288-69-1
- Chemical name: Immunoglobulin G1, anti-human p185 neu receptor human-mouse monoclonal recombinant human monoclonal antibody (r-hu-Mab) human epidermal growth factor receptor 2 (HER2) g1-chain, disulfide with human-mouse monoclonal r-hu-Mab HER2 light chain, dimer
- Company or Laboratory Code: MYL-1401O
- Other Names: Bmab-200, Hercules

3.2.S.1.2 Structure

The relative molecular mass of MYL-1401O is 148054±15 Da. MYL-1401O consists of 1328 amino acids, with LCs and HCs comprised of 214 and 450 amino acids, respectively. The amino acid sequences for the HCs and LCs of MYL-1401O are shown in the table below (glycosylation at Asn 300 of the HC is indicated by the red N).

Figure 3.2.S.1.2/ 1: Amino Acid Sequence of Light and Heavy Chains*

```

Bmab-200 PGS LC:
      23
1  DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQK GKAPKLLIYS
      |-----|
      88
51  ASFLYGVPS RFGSRSRGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ
      |-----|
      134
101  GTKVEIKRTV AAPSVEIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
      |-----|
      194
151  DNALQSGNSQ ESVTEQDSKD STYLSLSTLT LSKADYEKHK VYACEVTHQG
      |-----|
      214
201  LSSPVTKSFN RGEC-----|

Bmab-200 PGS HC:
      22
1  EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR
      |-----|
      96
51  IYPTNGYTRY ADSVKGRFRTI SADTSKNTAY LQMNLSRAED TAVYYCSRWG
      |-----|
      147
101  GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
      |-----|
151  DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT
      |
      *  *
      |
      203      223  229  232
1201  YICNVNHKPS NTKVDKKEVP KSCDKTHTCP PCPAPELLGG PSVFLFPPPK
      |-----|
      264
251  KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
      |-----|
      324
301  STYRVVSVLT VHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
      |-----|
      370
351  VYTLPPSREE MTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV
      |-----|
      428
401  LDSDGSEFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
      |-----|
    
```

--- indicates disulphide bond
 Underline bold indicates complementarity-determining regions
 Cysteine (C) 229 & 232 marked with asterisks (*) are involved in inter-heavy chain disulphide bond formation.
 HC: N300 = glycosylation site.
 *representation is with C-terminal lysine and without post-translational modification

(b) (4)

The HCs and LCs are covalently linked through inter-chain disulfide bonds and the expected disulfide linkages are provided in the table below.

Table 3.2.S.1.2/ 1: Expected Disulphide Linkages

Intra-light chain	LC _{Cys134} -LC _{Cys194}
	LC _{Cys23} -LC _{Cys88}
Intra-heavy chain	HC _{Cys22} -HC _{Cys96}
	HC _{Cys264} -HC _{Cys324}
	HC _{Cys370} -HC _{Cys428}
	HC _{Cys147} -HC _{Cys203}
Inter-chain	HC _{Cys229} -HC _{Cys229} / HC _{Cys232} -HC _{Cys232}
	HC _{Cys223} -LC _{Cys214}

Cys = cysteine

3.2.S.1.3 General Properties

The physical and chemical properties of MYL-1401O drug substance (DS) include a pH of 5.7-6.3, an isoelectric point of the main peak of the antibody of 8.2-8.8 (capillary isoelectric focusing), and an extinction coefficient of 1.48 (theoretical and experimentally confirmed).

The recognized mechanisms of action of trastuzumab are initiated through the binding of the antibody Fab region to HER2 on the target cell and binding of the antibody to Fc receptors on immune effector cells.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The MYL-1401O DS manufacturing and testing sites and corresponding responsibilities are provided in the following table.

Table 3.2.S.2.1/ 1: Details of the Sites Used for Manufacture and Testing of MYL-1401O Drug Substance

Name and Address	Responsibility	Facility Establishment Identifier (FEI#) Number and Data Universal Numbering System (DUNS)
(b) (4)		

Reviewer Comment: A requirement for the lyophilized material to be largely intact cake was added upon request, because and the data provided to support stability of MYL-1401O appear to have been obtained using material in the form of a cake, not powdered material.

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

Most of the analytical methods included in the MYL-141O DP release specifications are the same as those used for the release of MYL-1401O DS. Additional compendial DP methods include visible particle and sub visible particle testing, moisture content, osmolality, uniformity of fill, and sterility. Additional non-compendial methods include an anti-idiotypic antibody ELISA for identity and evaluation of PEG 3350 content using SEC-HPLC.

Anti-idiotypic antibody ELISA for Identity

The identity test is conducted using a sandwich ELISA method in which 96-well assay plates are coated with an antibody raised against a specific idioype located in the complementary determining region of the MYL-1401O antibody. Reconstituted MYL-1401O DP samples, non-specific negative control antibody, diluent blank, and the MYL-1401O IRS are added to the plates and allowed to bind. The assay plates are then incubated with anti-human Fc-specific HRP conjugated antibody, which will form a complex with MYL-1401O bound to the anti-idiotypic MYL-1401O antibody. Colorimetric detection is facilitated by the addition of TMB, and samples are read at 450 nm. The assay acceptance criteria are that the OD of the control should be ≥ 10 times greater than that of the blank, the negative control sample should be twice or equal to the OD of the blank, and the test sample OD should be comparable to the OD of the positive control. If the resulting OD complies with the acceptance criteria then the sample is reported as being positively identified as MYL-1401O DP.

The validation parameters evaluated include specificity and precision (repeatability and intermediate precision), and the samples evaluated were MYL-1401O IRS-^{(b) (4)}, negative control Bmab-100 IRS, which is a biologic with similar structure, and negative control BMO-2 IRS.

Specificity: Specificity was evaluated by measuring the OD of MYL-1401O IRS-^{(b) (4)}, Bmab-100 IRS and BMO-2 IRS at concentrations of either 100 ng/ml or 1.56 ng/ml. Only MYL-1401O IRS-^{(b) (4)} had a detectable OD at the lowest concentration, and at the highest concentration the MYL-1401O IRS-^{(b) (4)} had ODs in the range of 1.802-1.927, while the negative controls ODs ranged from 0.018 to 0.053. The OD values resulting from the non-specific controls were similar to the OD values reported for runs of diluent only of 0.016-0.035. The CV was 4% for three runs of MYL-1401O IRS-^{(b) (4)} 100 ng/ml.

Precision: Repeatability was assessed by evaluating six individual samples of MYL-1401O IRS-^{(b) (4)} at a concentration of 100 ng/ml in triplicate over 3 days by the same analyst using the same equipment. The CV values were 5% each day and 6% across all days.

Intermediate precision was evaluated intra-day by two analysts using MYL-1401O IRS-^{(b) (4)} at 100 ng/ml. The validation report stated that the two negative control antibodies were included in the intermediate precision study, but no data points were provided in the report. The CV was 6%.

Reviewer comment: *Considering that the purpose of the assay is to identify the MYL-1401O DP for release, the method validation is acceptable.*

PEG 3350

The method used to quantify PEG 3350 is based on an HPLC separation with detection using a charged aerosol detector (CAD). System suitability is based on PEG 3350 standards, and the sample concentration is calculated from a standard curve.

The method was validated using DS and DP samples.

Specificity: No diluent interference was detected.

Linearity, Range, and Accuracy: Linearity was evaluated for preparations from 0.1-0.3 mg/ml. Recovery was 98.6-101.5%, and the R² value was 0.99. These concentrations were evaluated for range; the RSDs were <1% (LOD/LOQ was not assessed further).

Precision: System Precision: The RSD for PEG 3350 replicates was <1%.

Repeatability: The RSDs of six preparations of DS and DP were 0.89% and 1.37%, respectively.

Intermediate precision: The repeatability study was performed on a different day by a different analyst using different materials. The RSDs across studies were 1.91% and 2.57% for DS and DP, respectively.

Robustness: The stability of the standard solution, sample solution, mobile phase, flow rate, column, acetonitrile concentration, and TFA concentration were assessed.

Reviewer comment: *The method is sufficiently suitable its purpose.*

Protein content

The recoverable protein content is determined for each vial of MYL-1401O DP by multiplying the extractable volume present in a vial post-reconstitution with 20 ml of WFI by the estimated protein concentration.

Reviewer Comment: *We defer to DMA regarding the adequacy of the endotoxin, sterility, and container closure integrity assays and assay validation.*

3.2.P.5.4 Batch Analyses

Batch analysis results were provided for three pre-validation batches manufactured by DS manufacturing process B, three PV batches manufactured using the intended commercial scale process C, and two post-process validation batches also manufactured using process C.

Reviewer comment: *The batch analysis data demonstrate consistency in the MYL-1401O DP clinical (Process B) and commercial (Process C) scale manufacturing processes. No major trending was noted in the quality attributes assessed and each batch met the pre-defined acceptance criteria.*

3.2.P.5.5 Characterization of Impurities

Other than potential leachables from product contact materials, the MYL-1401O DP manufacturing process does not introduce any product or process-related in addition to those introduced during the MYL-1401O DS manufacturing process.

3.2.P.6 Reference Standards or Materials

The reference standard used for the evaluation of MYL-1401O DP is the same reference standard used for MYL-1401O DS and is described in Section 3.2.S.5.

3.2.P.7 Container Closure System

The primary packaging of the MYL-1401O DP includes a 50 ml (b) (4) glass vial that is closed with a 20 mm grey (b) (4) stopper and sealed with a 20 mm lavender flip-off aluminum cap. The secondary packaging consists of a (b) (4) cardboard box.

The vials are compliant with USP <660> and Ph. Eur. 3.2.1.

The (b) (4) stoppers are compliant with USP <381> and Ph. Eur. 3.2.9. The stopper and (b) (4) meet the requirements of USP <87> (bioreactivity) and the EU directive for heavy metals.

The specifications for the vials and stoppers include visual examination, numerous evaluations of dimensions and weight, and USP or Ph.Eur. tests.

3.2.P.8 Stability

3.2.P.8.3 Stability Data

“Registration” stability studies were conducted using the three MYL-1401O DP PV batches. The storage conditions evaluated included the long term condition of 5±3°C and an accelerated condition of 25±2°C (60% RH ± 5% RH); up to 6 months of data were provided for both storage conditions. The specification tests are included for timepoints at 3, 6, 9, 12, 18, 24, 36, and 48 months for long term storage. The proposed shelf-life for MYL-1401O is 48 months when stored at 5±3°C.

Reviewer comment: The registration stability study protocol does not include an evaluation of ADCC activity. Mylan was requested to provide any available data to support stability with respect to this potency attribute. A stability update was also requested, and data through 12 months were provided; the supporting stability data were also updated, and the proposed shelf-life was updated to correspond to the supporting data timepoint.

The 12 month stability results for storage at 5±3°C showed no significant changes or trending in any of the quality attributes evaluated. Following six months of storage at 25±2°C, the following changes were observed:

- A 0.5% increase in HMWS assessed by SEC-HPLC.

- An increase in acidic variants of ~1.5%, an increase in basic variants of ~1.5%, and a decrease in main variant of ~1%.
- A minor decrease of ~0.2% was observed in PEG 3350 content.

Supportive stability study data were also provided for MYL-1401O DP batches that were manufactured from MYL-1401O DS produced using Process B. The stability protocol included storage under long-term conditions for up to 48 months, under accelerated conditions for 6 months, and under stressed conditions ($40\pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$) for 6 months.

Following 48 months storage at $5\pm 2^{\circ}\text{C}$: The primary change noted was a basic species increase of 1.1-1.9%; there was also an acidic species increase of 0.4-0.9%. While HMWP consistently increase slightly, this change is not practically significant. No significant changes or trending was observed for the remaining product quality attributes evaluated.

Following 6 months storage at $25\pm 2^{\circ}\text{C}$:

- An increase of ~0.4% HMWS was shown for all three batches.
- An increase of ~3% basic species and a decrease of ~2% main species were shown for all three batches.

Following 6 months storage at $40\pm 2^{\circ}\text{C}$:

- An increase of ~3% HMWS was shown for two batches, and an increase of ~0.4% was shown for the other batch; a corresponding decrease was also observed in monomer content.
- An increase of ~0.3% p100.
- An increase of ~21% basic variant was observed for two batches, and an increase of ~3% for one batch; a corresponding decrease of ~3-23% main peak was observed.

Reviewer comment: *The stability studies indicate changes in charged species, similar to the hold and stability studies for DS, and the specific attributes that are changing have not been identified. While the rates of degradation are difficult to assess using stressed studies with rapid changes, the comparative temperature stress stability data presented in Tables 3.2.P.8.3/17 and /19 indicate that MYL-1401O basic species may increase faster than US-Herceptin or EU-Herceptin basic species, and the data presented in Table 3.2.P.8.3/31 indicate that MYL-1401O may be more sensitive to oxidative stress. In addition to the requests for information discussed in the DS section, Mylan was requested to identify the product quality attributes that changed differentially, but no additional information could be provided. The forced degradation studies are discussed below in greater detail in Section 3.2.R.4 Analytical Similarity Assessment: Comparative Stability.*

Overall, given the real time and accelerated condition stability studies, the supportive stability study data were consistent with the registration stability study, and the manufacturing processes, comparability study, and stability studies are sufficient to support establishment of the proposed expiry period of 48 months at $5\pm 3^{\circ}\text{C}$.

A temperature excursion study was designed to evaluate the stability of MYL-1401O DP under various conditions outside of the ideal long-term storage condition. A single batch of MYL-1401O DP was included in the study. The temperature excursion protocol included three cycles of storage at -20°C for 24 h followed by storage at 25°C or 40°C for 48 h. These cycles were followed by or preceded by 48 months of storage at 5°C. Appearance, pH, protein concentration, moisture content, sub-visible particles, purity (SEC, CE-SDS, IEX) and potency (inhibition of proliferation) were evaluated.

The results provided showed no significant changes or trends in the product quality attributes assessed immediately following three cycles; however the studies, as described, are not complete. There were minor changes in HMWS and basic and acidic variants.

Reviewer comment: *The temperature excursion study data provided in Section 3.2.P.8.3.4.2 do not appear to be consistent with the studies described in Section 3.2.P.8.1.2.3.2; it may be that the studies are not complete. Mylan was requested to clarify the nature of the data provided in Section 3.2.P.8.3 and provide any additional data related to the studies described in Section 3.2.P.8.1. In the response, Mylan clarified that the purpose of the studies was to assess the DP quality attributes following temperature excursions and it was also clarified that the studies are not complete. Mylan stated the outstanding stability data would be provided in an annual report.*

The results that are currently available are similar to the results of other studies and suggest that MYL-1401O DP product quality will not be significantly impacted if the product is exposed to limited temperature excursions.

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

Mylan committed to completing the ongoing stability studies for the three registration batches and commits to placing at least one commercial batch of MYL-1401O DP onto the long-term stability protocol described below annually, if a MYL-1401O manufacturing campaign was conducted.

Table 3.2.P.8.2/ 1: Annual Stability Protocol for Commercial Batches of MYL-1401O Drug Product

Parameter/Test	Annual Stability at 5°C ± 3°C (in months)				
	0	12	24	36	48
Appearance (lyophilized product)	x	x	x	x	x
Clarity/Opalescence of reconstituted product	x	x	x	x	x
Color of reconstituted product	x	x	x	x	x
pH of reconstituted solution	x	x	x	x	x
Protein concentration by ultraviolet spectrophotometry	x	x	x	x	x
Quantity content of protein	x	x	x	x	x
Visible particles	x	x	x	x	x
Subvisible particles	x	x	x	x	x
Moisture content	x	x	x	x	x
Polyethylene glycol 3350/Macrogol 3350	x	x	x	x	x
Osmolality	x	x	x	x	x
Purity by SEC-HPLC	x	x	x	x	x
Purity by CE-SDS (under non-reducing condition)	x	x	x	x	x
Purity by CE-SDS (under reducing condition)	x	x	x	x	x
IEX HPLC	x	x	x	x	x
Biological activity (inhibition of proliferation assay by SK-BR-3)	x	x	x	x	x
Biological activity (HER2 binding assay by flow cytometry by SK-BR-3)	x	x	x	x	x
Container closure integrity test - Dye ingress test	-	x	x	x	x
Endotoxin	x	x	x	x	x
Sterility	x	x	x	x	x

x, Test performed; -, Test not performed

Reviewer comment: *The MYL-1401O DP post-approval stability protocol does not include an evaluation of ADCC activity. This is discussed in the DS section, above. In addition, as for DS, Mylan notes that if an OOS occurs, Mylan will report the deviation to the regulatory authorities and, if necessary, the DP batch will be withdrawn from the market. However, the annual stability lot covers all lots manufactured during the timeframe, so all relevant DP lots may need to be withdrawn from the market. Mylan will be requested to update the BLA to reflect this action. As discussed in Section 3.2.S.7.2, Mylan confirmed that the appropriate actions will be taken and updated the BLA accordingly.*

3.2.P DRUG PRODUCT - BACTERIOSTATIC WATER FOR INJECTION (BWFI)
For reconstitution of lyophilized MYL-1401O

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

3.2.P.1.1 Description of the Dosage Form

The BWFI is a colorless, transparent, USP-grade sterile non-pyrogenic WFI with 1.1% benzyl alcohol (USP) supplied in 20 ml (b) (4) glass vials closed with a (b) (4) stopper and sealed with a plastic flip-off cap with aluminum seal. The BWFI is co-packaged with MYL-1401O DP for use in reconstitution of the lyophilized MYL-1401O DP to yield a multi-use solution containing 21 mg/ml of DP.

An overfill of (b) (4) ml is included in each vial of BWFI to allow for sufficient withdrawal of the appropriate reconstitution volume.

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Registration stability studies were conducted using the three BWFI PV batches. The storage conditions evaluated were long term storage at 2-8°C and accelerated conditions of 25±2°C/60% RH ± 5% RH; 3 months of data were provided for both storage conditions. The proposed shelf-life is ^(b)₍₄₎ months when stored alone at ^(b)₍₄₎ is recommended. The following table shows the registration stability study protocol.

Table 3.2.P.8.1/ 2: Registration Stability Protocol for BWFI, USP (1.1 % Benzyl Alcohol)

Parameter/Test	Long Term Storage at 5°C ± 3°C (in months)									Accelerated Storage at 25°C ± 2°C / 60% RH ± 5% RH (in months)									
	0	3	6	9	12	18	24	36	48	0	1	2	3	6	9	12	18	24	
Appearance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
pH	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Antimicrobial agents-Benzyl alcohol content by GC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Particulate matter in injection	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Bacterial endotoxin	x	NA	NA	NA	x	NA	x	x	x	x	NA	NA	NA	NA	NA	x	NA	x	
Calcium test	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbon Dioxide test	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sulphate test	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sterility	x	NA	NA	NA	x	NA	x	x	x	x	NA	NA	NA	NA	NA	x	NA	x	
Container closure integrity test-Dye ingress test	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Antimicrobial effectiveness test ^a	x ¹	NA	NA	NA	NA	NA	NA	NA	x	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

x - Test as part of the stability protocol; NA - Not applicable as it was not part of the protocol; ¹ - Test done outside the stability protocol

^a Antimicrobial effectiveness test intended to be performed only on the 3 commercial scale process validation batches.

Reviewer comment: DMA will review the more critical aspects of this protocol; for more general parameters, the protocol appears to be acceptable.

The stability results for BWFI stored under both long term and accelerated conditions indicated no change in the attributes evaluated following three months of storage.

Reviewer comment: The proposed shelf-life for the BWFI is ^(b)₍₄₎ months storage at ^(b)₍₄₎ condition; however, only 3 months data were provided. The data were updated to include the 12 month time point. We defer to DMA for a determination on if the proposed shelf life of the BWFI with respect to the stability of the antimicrobial agent is acceptable; the DMA reviewer stated that the data are acceptable. Because the expiration date for co-packaged components is based ^(b)₍₄₎

^(b)₍₄₎ Mylan was requested to update the BLA to clearly indicate how the expiration date listed on the DP carton will be derived. Additionally, based on discussions with Mylan, it was noted that if they would like to implement a revised BWFI stability protocol with intermediate timepoints to enable earlier updates to the BWFI expiry period, the amended protocol could be submitted to the BLA. In the response, Mylan stated the expiry of the DP carton will be based on the ^(b)₍₄₎.

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

Mylan committed to completing the ongoing stability studies for the three registration batches and commits to placing at least one commercial batch of BWFI, if manufactured, on the long term stability protocol annually (see Table 3.2.P.8.2/1, below).

Table 3.2.P.8.2/ 1: Annual Stability Protocol for Bacteriostatic Water for Injection, USP (1.1% Benzyl Alcohol)

Parameter/Test	Annual Stability at 5°C ± 3°C (in months)				
	0	12	24	36	48
Appearance	x	x	x	x	x
Antimicrobial agents - benzyl alcohol content by gas chromatography	x	x	x	x	x
pH	x	x	x	x	x
Particulate matter in injection	x	x	x	x	x
Calcium test	x	x	x	x	x
Carbon dioxide test	x	x	x	x	x
Sulphate test	x	x	x	x	x
Bacterial endotoxin	x	x	x	x	x
Sterility	x	x	x	x	x
Container closure integrity test - Dye ingress test	-	x	x	x	x

x, Test performed
 -, Test not performed

Reviewer comment: The post-approval stability protocol appears acceptable.

3.2.A.2 Adventitious Agents Safety Evaluation

Reviewer comment: Raw materials of biological origin, cell bank testing, and unprocessed bulk testing were discussed in Sections 3.2.S.2.3 and 3.2.S.2.4.

Viral Clearance Overview and Selection of Viruses

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer comment: The per dose safety factor for MYL-1401O is acceptable.

3.2.R Regional Information

3.2.R.1 Executed Batch Records

Copies of the batch records for the DS, DP, and BWFI PV batches were provided in the BLA.

Reviewer Comment: The information provided is acceptable. Batch records for DS and DP were also reviewed during the PLI at (b) (4), and comments regarding discrepancies were noted in the EIR and Form 483 that was issued to the facility.

3.2.R.4 Analytical Similarity Assessment

3.2.R Analytical Similarity

Herceptin (trastuzumab) has been marketed in the United States (US) as a multi-dose vial containing 420 mg of lyophilized trastuzumab, and in the European Union (EU) Herceptin is marketed as a single-dose vial containing 150 mg of lyophilized trastuzumab. Only subsequent to the submission of this BLA was a 150 mg Herceptin presentation approved in the US. As such, Mylan developed 150 mg and 420 mg presentations of MYL-1401O, and the 420 mg presentation, consistent with the US-licensed Herceptin (US-Herceptin) available during MYL-1401O development, is the subject of the current licensing application. Mylan conducted a supportive clinical pharmacokinetic (PK) study (MYL-HER-1001) and a confirmatory study (MYL-HER-3001) comparing MYL-1401O 150 mg DP to EU-Herceptin. Clinical data from a

comparative clinical PK study (MYL-HER-1002) using MYL-1401O 150 mg, EU-Herceptin and US-Herceptin were also provided in support of MYL-1401O licensure.

The analytical data are intended to support a demonstration of highly similar between MYL-1401O (420 mg) and US-Herceptin (420 mg). Because the comparator used in the confirmatory clinical study was EU-Herceptin (150 mg), this product was also included in the similarity assessment to establish the analytical portion of the scientific bridges between MYL-1401O and EU-Herceptin, MYL-1401O and US-Herceptin, and US-Herceptin and EU-Herceptin. Additionally, because only MYL-1401O 150 mg DP was included in the key clinical studies, analytical comparability data between MYL-1401O 150 mg and 420 mg DP were provided (Biosimilarity Comparability Report, Technical Report #CDL/TR/BR.14.5002/16/050). Both MYL-1401O 150 mg and 420 mg DP lots were included in the analytical similarity assessment. Advice from the Agency regarding combining data from the two MYL-1401O DP presentations in the analytical similarity assessment was conveyed to Mylan during the Type B meeting held in April 2012 and the Type 2/4 meeting held in September 2016; inclusion of both presentations in the analytical similarity assessment was to be contingent upon adequate comparability between the 150 mg and 420 mg MYL-1401O DP.

Reviewer comment: During the review cycle, the US-Herceptin labeling was revised to state a content of 420 mg, rather than 440 mg. Because MYL-1401O was developed to be similar to US-Herceptin, no changes needed to be made to the MYL-1401O DP manufacturing process as a result of the labeling change. Therefore, this change does not impact the comparability or analytical similarity data; however, the figures and tables included in this review refer to the MYL-1401O 440 mg presentation.

Also during the review cycle, numerous corrections to the analytical similarity data were submitted in response to information requests. The data presented reflect the final update (version 4 of the Comparability and Analytical Similarity Assessment for MYL-1401O).

Discussions of the analytical methods used in both the comparability and analytical similarity assessments are included in Section 3.2.S.3.1.6 and 3.2.S.4.3 of the review.

Analytical comparability between MYL-1401O 420 mg DP and MYL-1401O 150 mg DP

The DS manufacturing processes for MYL-1401O 150 mg and 420 mg DP are the same; however, the DP manufacturing processes include a different vial size and fill volume, and there are minor differences in the primary drying temperatures for lyophilization. Upon reconstitution with bacteriostatic water for injection (BWFI), both DP presentations have the same target protein concentration (21 mg/ml) and excipient concentrations.

MYL-1401O batches included in the comparability assessment

Data from 12 lots of MYL-1401O 150 mg (Table 6 below) and 8 lots of 420 mg (Table 7 below) manufactured from a total of 13 DS lots were included in the comparability assessment. The materials were manufactured between 2010 and 2015 at the (b) (4) L scale using either Process B (clinical) or Process C (the intended commercial process).

Of the 13 DS lots included, 5 were used to manufacture batches of both 150 mg and 420 mg DP, and 150 mg DP lot BS15003694 and 420 mg DP lot BS15005879 were both generated from the combination of the same 2 DS lots.

Reviewer comment: *It is appropriate to include DP lots manufactured from the same DS (or multiple DS) lots in the comparability assessment, because it allows for a more direct assessment of differences in quality attributes likely resulting from differences in the DP manufacturing processes (i.e., lyophilization cycle differences).*

Table 6: List of MYL-1401O 150 mg Batches with the Purpose for Which the Batch was Manufactured

S. No	MYL-1401O DS Batch No	MYL-1401O DP (150mg) Batch No	Date of Manufacturing	Purpose
1	DB-F10-F02-003	DEVBV10-0001	Jun/10	Non-clinical study (monkey tox study)
2	DB-P02-F11F02-005	DEVBV11-0007	Nov/11	Supporting Stability data for Phase III
3	DB-P02-F11F02-006	DEVBV11-0008	Nov/11	Supporting Stability data for Phase III
4	DB-P02-F11F02-007	DBBMPTV11-0001	Dec/11	Supporting Stability data for Phase III
5	DB-P02-F11F02-008	DBBMPTV12-0001	Apr/12	Reference standard batch
6	DB-P02-F12F02-001	DBBMPTV12-0003	Jul/12	Phase I batch (MYL-Her-1002); Phase III clinical batch (MYL-Her-3001)
7	DB-P02-F12F02-002	DBBMPTV12-0005	Oct/12	Phase III clinical batch (MYL-Her-3001)
8	DB-P02-F12F02-003	BS14007346	Aug/14	Phase III clinical batch (MYL-Her-3001)
9	BS14011367	BS14012746	Mar/15	Phase III clinical batch (MYL-Her-3001)
10	BS15000304 & BS15002083	BS15003694	Aug/15	Process validation batch
11	BS15000673	BS15003580	Aug/15	Process validation batch
12	BS15000304	BS15003340	Aug/15	Process validation batch

Table 7: List of MYL-1401O 440 mg Batches used for comparability assessment

S. No	MYL-1401O DS Batch No	MYL-1401O DP (440mg) Batch No	Date of Manufacturing	Purpose
1	DB-P02-F11F02-006	DBBMPPV12-0001	Feb/13	Development batch, To generate supporting stability data
2	DB-P02-F11F02-007	DBBMPPV12-0002	Feb/13	Development batch, To generate supporting stability data
3	DB-P02-F11F02-005	DBBMPPV12-0003	Mar/13	Development batch, To generate supporting stability data
4	BS15000673	BS15005600	Nov/15	Process validation batch
5	BS15002083	BS15005677	Nov/15	Process validation batch
6	BS15000673& BS15000304	BS15005879	Nov/15	Process validation batch
7	BS15004184	BS15006002	Dec/15	Post- process validation batch
8	BS15004444	BS15006421	Dec/15	Post- process validation batch

Quality attributes included in the comparability assessment

The following attributes were assessed to demonstrate comparability between the 150 mg and 420 mg MYL-1401O: pH, sub-visible particles, moisture content, protein content, osmolality, size variants, charge variants, PEG-3350 content, reconstitution time, and biological activity (inhibition of proliferation and HER2 binding). Additional characterization was conducted to evaluate ADCC activity, FcγRIIIa high affinity isoform 158V binding, oxidation, higher order structure, and disulfide bonding.

Reviewer comment: *The list of attributes included for the evaluation of the 150 mg and 420 mg presentations are adequate for the assessment of comparability.*

Statistical approach used in the comparability exercise

The statistical approach taken to establishing comparability between MYL-1401O 150 mg and 420 mg was based on quality ranges (QR) derived from the mean $\pm$ 2 or 3 SD of the 150 mg presentation data (the MYL-1401O DP presentation used in the nonclinical and clinical studies).

Reviewer comment: *During a Type 2/4 meeting, Mylan was advised to evaluate the 420 mg MYL-1401O lots against a QR based on the 150 mg lots, because the 150 mg, not the 420 mg, lots were used in the key clinical studies. Therefore, the data provided in the submission are reflective of this advice. However, because Mylan is seeking licensure of the MYL-1401O 420 mg presentation, it is also important to determine if the two presentations are comparable based on the 420 mg QR. Therefore, FDA conducted an independent analysis of the data provided using the QR based on the 420 mg lots.*

The QRs applied to quality attributes considered to be highly critical or impacted by the lyophilization process and/or were assessed using a method with variability of $>$ 15% were calculated using the mean $\pm$ 2SD, with the exception of SEC-HPLC size variants and charge variants, which were evaluated against $\pm$ 3 SD. All other attributes were analyzed using $\pm$ 3SD. No statistical analyses were applied to the DSC or disulfide bridging data. The comparability acceptance criterion defined by Mylan was $>$ 90% of the batches evaluated are within the QR of the quality attribute.

Reviewer comment: *Aggregate formation and charge heterogeneity are critical quality attributes that have some potential to be impacted by variations in the manufacturing process, and therefore, the testing results will be more fully evaluated than simply using the $\pm$ 3SD QR.*

Comparability Results

5.1.1 pH

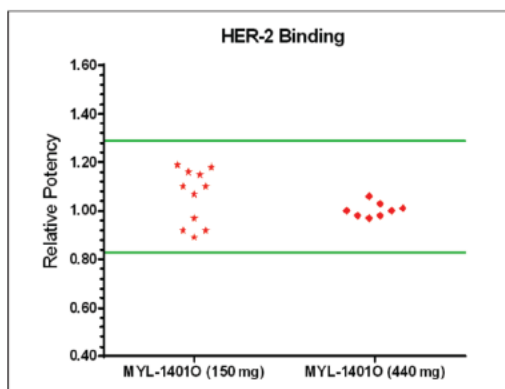
The range of pH values for MYL-1401O 150 mg DP lots was 5.94-6.18 and the range for MYL-1401O 420 mg DP lots was 5.98-6.07.

Reviewer comment: *The pH of the 150 mg and 420 mg DP lots are comparable.*

5.1.2 HER2 Binding

The ability of MYL-1401O to bind the HER2 receptor was assessed using the SKBR3-based flow cytometry assay. Eleven lots of MYL-1401O 150 mg and 8 lots of MYL-1401O 420 mg exhibited average relative binding ranges from 0.89-1.19 and 0.97-1.06, respectively (Table 12 and Figure 2, below). The 420 mg lots were within the 150 mg-based QR criteria (based on $\pm$ 2 SD).

Figure 2: Scatter Plot Distribution of Relative HER2 Binding of MYL-1401O (440 mg and 150 mg) Lots



Green lines represent the Mean $\pm$ 2SD range derived from the MYL-1401O 150 mg Lots

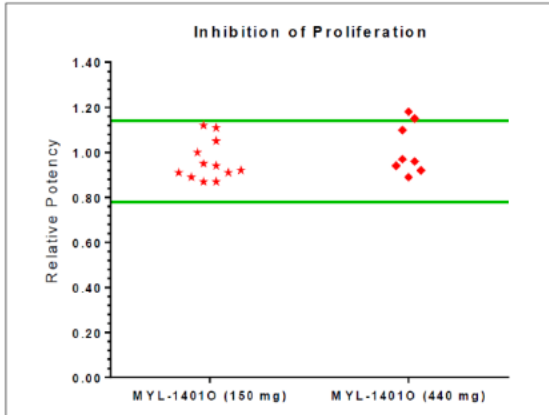
Reviewer comment: In response to the information request dated March 27, 2017, Mylan provided the genealogy and qualification data for the IRS used throughout the MYL-1401O development program (Comparability and Analytical Assessment Report Annexure 3). Mylan used multiple IRS in the potency/functional assays, including some assays used to assess the 150 mg lots included in the comparison of the 150 mg and 420 mg presentations. The IRS had not been qualified under protocols intended to prevent drift, and the relative potency values were variable between IRS. Therefore, it is difficult to directly compare results from assays for which different IRS were used. As such, a separate evaluation of the potency data derived from the MYL-1401O 150 mg lots that were assessed against IRS QC/Q8/LS/001/03 (the IRS used in the analytical similarity assessment and for release of PV batches) will be considered where applicable.

The 420 mg lots were all with the QR based on the 150 mg lots assessed using the main IRS. Because there was such little variability in the 420 mg lots, based on a 420 mg QR of 0.915-1.093, only 4 out of the 11 150 mg lots met the criteria. However, the remaining 150 mg lots were very slightly outside the QR (0.89-1.19 overall range for 150 mg). Three of the five 150 mg lots evaluated using the main IRS were within the 420 mg QR criteria. A comparison of the 150 mg and 420 mg batches derived from the same DS lot (batch BS15000673) and evaluated using the same IRS showed that the 150 mg lot (BS15003580) tested at a lower relative binding level (0.89) than the 420 mg lot (BS15005600; 1.01). Although only shown for one lot of each presentation, this comparison may suggest that assay variability impacted the analysis. The data provided in the validation report for the HER2 binding assay show similar levels of variability among the same lots analyzed on different days and/or by different analysts (see Section 3.2.S.4.3). As discussed below, adequate comparability was demonstrated between the 150 mg and 420 mg DP lots with respect to inhibition of proliferation and ADCC activity, which both require HER2 binding. Considering this assessment, the differences in HER2 binding may be attributed to variability in DS in addition to assay variability. Therefore, the differences between the two presentations are not likely due to impact of the DP manufacturing processes and do not preclude the use of the 150 mg presentation to support analytical similarity.

5.1.3 Inhibition of Proliferation

In the cell-based inhibition of proliferation assay, two 420 mg lots had activity slightly higher than the upper limit of the 150 mg based QR (± 2 SD; Table 13 and Figure 3, below). The potency range was 0.87-1.12 for the MYL-1401O 150 mg DP lots and 0.89-1.18 for the MYL-1401O 420 mg DP lots.

Figure 3: Scatter Plot Distribution of Relative Potency of MYL-1401O (440 mg and 150 mg) Lots



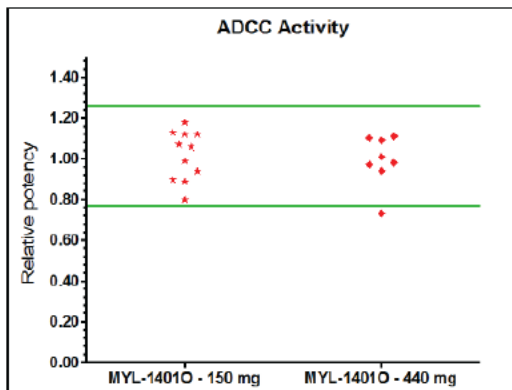
Green lines represent the Mean $\pm$ 2SD range derived from the MYL-1401O 150 mg Lots

Reviewer comment: One additional 420 mg lot was outside the QR based on the 150 mg lots assessed using the main IRS. All of the 150 mg DP lots were within the QR based on the 420 mg DP lots (0.79-1.24). Given the potential for a minor amount of assay variability, these results demonstrate comparability in inhibition of proliferation between the 150 mg and 420 mg lots.

5.1.4 ADCC

The ADCC range was 0.80-1.18 for the MYL-1401O 150 mg DP lots and 0.73-1.11 for the MYL-1401O 420 mg DP lots (Table 14 and Figure 4, below). One 420 mg DP lot had a relative potency (0.73) below the 150 mg based QR (lower limit – 0.77) and outside of the ADCC assay acceptance criterion of (b) (4).

Figure 4: Scatter Plot Distribution of Relative ADCC Activity of MYL-1401O (440 mg and 150 mg) Lots



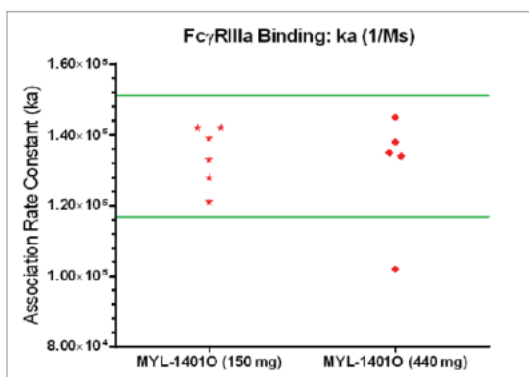
Green lines represents the Mean $\pm$ 2SD range derived from the MYL-1401O 150 mg Lots

Reviewer comment: All 150 mg DP lots were within the 420 mg based range ($\pm 2SD$; 0.74-1.24). The 420 mg lot with low ADCC activity (BS15006002) also had a lower Fc γ RIIIa equilibrium dissociation constant (148 nM, see discussion below). The corresponding DS data reveal no obvious differences (e.g., in fucosylation) that would contribute to the low relative potency. No ADCC data are provided for the corresponding DS lot (BS15004184). Based on the correlative Fc γ RIIIa data, it is not likely that the low relative ADCC potency value is due to assay variability; however, it indicates the difference is related to DS, rather than the DP presentation. All ADCC analyses were performed using the main IRS. The ADCC activity data are comparable between the 150 mg and 420 mg lots.

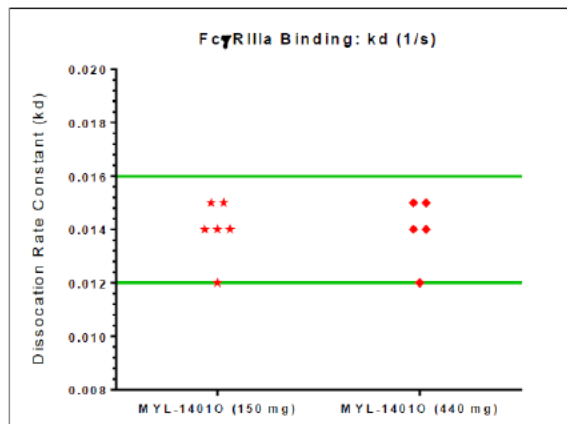
5.1.5 Fc γ RIIIa-V158 binding

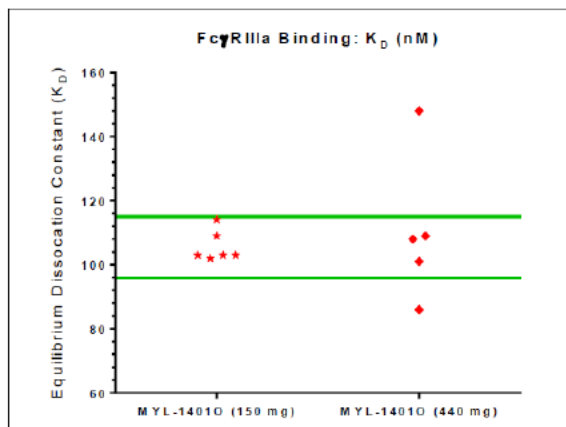
SPR was used to determine the kinetics of the interaction between MYL-1401O and Fc γ RIIIa (V158 isoform). The results for six lots of MYL-1401O 150 mg and five lots of MYL-1401O 420 mg were presented in Table 15. The ranges of six lots of MYL-1401O 150 mg were: k_a – 1.21×10^5 - 1.42×10^5 1/Ms, k_d – 0.012-0.015 1/s, and k_D – 102-114 nM. The ranges of five lots of MYL-1401O 420 mg Fc γ RIIIa were: k_a – 1.02×10^5 - 1.45×10^5 1/Ms, k_d – 0.012-0.015 1/s, and k_D – 86-148 nM (Table 15 and Figure 5, below).

Figure 5: Scatter Plot Distribution of Fc γ RIIIa Binding (k_a) of MYL-1401O (440 mg and 150 mg) Lots



Green lines represent the Mean $\pm$ 2SD range derived from the MYL-1401O 150 mg Lots





Reviewer comment: All 150 mg DP lots were within the 420 mg-based QR criteria. The 420 mg lots have greater variability in FcγRIIIa binding kinetics compared to the 150 mg lots; this is driven predominantly by one 420 mg lot. Specifically, lot BS15006002 has a k_D value of 148 nM, which correlates with low ADCC activity (0.73; outside the QR), and lot BS15005600 which has a k_D value of 86 nM correlates with high ADCC activity (1.11). The 420 mg lot BS15005600 and the 150 mg DP lot BS15003580 were derived from the same DS lot. Lot BS15003580 has a k_D of 103 nM. These data suggest that the variability in the binding kinetics observed within the 420 mg lots and between the two presentations, is likely due in part to assay variability, which is not unexpected for SPR-based assays. The FcγRIIIa binding kinetics between the two presentations are comparable.

5.1.6 Osmolality

The range of osmolality values was 92-110 mOsmol/kg for 12 150 mg lots and 94-110 mOsmol/kg for 8 420 mg lots. The ranges observed for both DP presentations are similar.

Reviewer comment: The osmolality data support comparability between the two presentations.

5.1.7 Subvisible particle content

The ranges of SVPs for 12 lots of MYL-1401O 150 mg were: 40-460 ≥ 10 μm and 1-28 ≥ 25 μm; the ranges for 8 lots of MYL-1401O 420 mg were: 144-1717 ≥ 10 μm and 1-67 ≥ 25 μm (Table 17). However, the values are reported on a per container basis. On a per ml basis, the ranges for MYL-1401O 150 mg are: 6-64 ≥ 10 μm and 0.1-3.9 ≥ 25 μm, and the ranges for MYL-1401O 420 mg are: 7-86 ≥ 10 μm, 0.05-3.35 ≥ 25 μm.

Reviewer comment: Based on the per ml assessment, the SVP levels are comparable between the two DP presentations.

5.1.8 Moisture content

The ranges of values for moisture content were 0.39-1.41% (w/w) for 12 MYL-1401O 150 mg DP lots and 0.15-0.83% (w/w) for 8 MYL-1401O 420 mg DP lots (Table 18 and Figure 8).

Reviewer comment: The moisture content of all MYL-1401O 420 mg DP lots were within the 150 mg QR. Eleven out of 12 lots were within the 420 mg QR. Overall, the residual water content data are comparable between the 150 mg and 420 mg DP lots.

5.1.9 PEG-3350 content

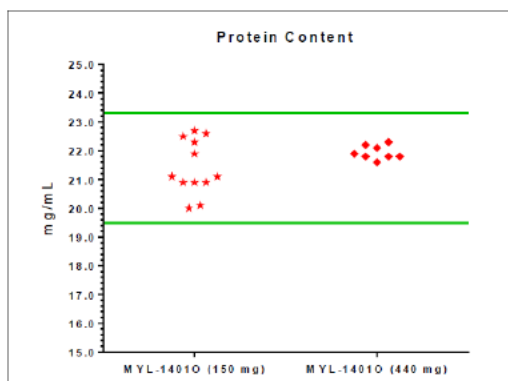
The range of the PEG-3350 content was 3.90-5.20 mg/ml for 11 150 mg DP lots and 4.20-5.45 for 8 420 mg DP lots (Table 19 and Figure 9).

Reviewer comment: Ten of the 150 mg lots were within both the 420 mg and 150 mg QRs; the single lot outside the range was just outside the lower limit. The overall PEG content is comparable between the 150 mg and 420 mg DP lots.

5.1.10 Protein content

The ranges of protein content were 20.0-22.7 mg/ml for 12 MYL-1401O 150 mg DP lots and 21.6-22.3 mg/ml for 8 MYL-1401O 420 mg DP lots (Table 20 and Figure 10, below).

Figure 10: Scatter Plot Distribution of Protein Content of MYL-1401O (440 mg and 150 mg) Lots



Green lines represent the Mean +/- 2SD range derived from the MYL-1401O 150 mg Lots

Reviewer comment: The 150 mg lots have greater variability in protein concentration. Only 4 out of the 12 150 mg lots were within the 420 mg QR (21.46-22.41 mg/ml). Based on a comparison of 150 mg and 420 mg DP lots manufactured from the same DS lots (listed below), it appears that the difference is due to the fill used for the 150 mg and 420 mg presentations.

- 150 mg DEVBV11-007 = 20.0 mg/ml vs. 420 mg DBBMPFV12-003 = 21.8 mg/ml
- 150 mg DEVBV11-0008 = 20.1 mg/ml vs. 420 mg DBBMPFV12-001 = 21.6 mg/ml
- 150 mg DBBMPTV11-0001 = 20.9 mg/ml vs. 420 mg DBBMPFV12-002 = 22.1 mg/ml
- 150 mg BS15003580 = 22.3 mg/ml vs. 420 mg BS15005600 = 22.2 mg/ml

The difference in protein concentration between the two DP presentations is a function of the manufacturing process and is not significant enough to impact the remainder of the comparability assessment.

5.1.11 HMWS and monomer (SE-HPLC)

The ranges for 12 150 mg DP lots were 0.19-0.47% HMWS and 99.5-99.8% monomer, and the ranges for 8 420 mg DP lots were 0.21-0.31% HMWS and 99.7-99.8% monomer (Table 21 and Figure 11).

Reviewer comment: *The variability in monomer and HMWS content between MYL-1401O 150 mg DP lots and 420 mg DP lots was consistent. Very minor variability was shown between 150 mg and 420 mg DP lots produced from the same DS batches, indicating that the differences in the manufacturing processes do not impact HMWS formation. The aggregate and monomer content of the 150 mg and 420 mg DP presentations are comparable.*

5.1.12 Fragments (CE-SDS non-reduced)

The ranges of fragment in 12 lots of 150 mg DP were 0.33-0.58% LC, 0.01-0.18% Fab/HC, 0.03-0.25% HL, 0.07-0.18% 2H, 0.64-1.80% 2H1L, 1.5-2.5% total fragment, and 97.5-98.5% monomer, and the ranges of fragment in 8 lots of 420 mg DP were 0.36-0.87% LC, 0.04-0.16% Fab/CH, 0.13-0.28% HL, 0.11-0.23% 2H, 1.00-1.78% 2H1L, 2.0-3.0% total fragment, and 97.0-98.0% monomer (Table 22 and Figure 12).

Reviewer comment: *The overall level of total fragments was higher in the 420 mg lots than the 150 mg lots. All of the 150 mg lots were within the 420 mg QR (± 3 sd), and 7 of the 420 mg lots were within the 150 mg QR (± 3 sd).*

The following analysis shows minor variability with no clear trend in total fragmentation between the 150 mg and 420 mg lots manufactured from the same DS batch:

- 150 mg DEVBV11-007 = 2.0% vs. 420 mg DBBMPFV12-003 = 2.5%
- 150 mg DEVBV11-0008 = 2.1% vs. 420 mg DBBMPFV12-001 = 2.2%
- 150 mg DBBMPTV11-0001 = 2.4% vs. 420 mg DBBMPFV12-002 = 2.4%
- 150 mg BS15003580 1.5% vs. 420 mg BS15005600 = 2.3%

The comparison of batches suggests that the minor differences in fragmentation may be attributed to variability of the DS manufacturing process.

5.1.13 Fragments by CE-SDS reduced

The ranges of fragment in 12 lots of 150 mg DP were 0.24-0.30% Ng-HC, 0.22-0.32% p100, and 99.4-99.5% HC+LC, and the ranges of fragment in 8 lot of 420 mg DP were 0.20-0.34% Ng-HC, 0.25-0.40% p100, and 99.3-99.5% HC+LC (Table 23 and Figure 13).

Reviewer comment: *All of the MYL-1401O 150 mg DP lots were within the 420 mg QR (based on $\pm 2SD$) and 7 420 mg lots were within the 150 mg QR. The CE-SDS reduced data are comparable between the 150 mg and 420 mg lots.*

5.1.14 Charge heterogeneity

The ranges for charge variants in eight lots of 150 mg DP were 22.4-24.9% acidic, 65.8-68.8% main, and 7.9-10.6% basic, and the ranges of eight lots of 420 mg DP were: 23.5-26.6% acidic, 64.6-67.6% main, and 7.4-9.8% basic (Table 24 and Figure 14).

Reviewer comment: *The MYL-1401O 420 mg DP lots have slightly higher levels of acidic variants and a minor decrease in main variants as compared to the 150 mg DP lots due to higher acidic variant content in 420 mg DP lots DBBMPFV12-0001 (26.3%) and DBBMPFV12-0002 (26.6%). No significant differences were observed in acidic, main peak or basic variant content between the 150 mg and 420 mg DP lots that were manufactured from the same DS, suggesting that charge heterogeneity is not impacted by changes in the DP manufacturing processes. All of the 150 mg lots are within the 420 mg QR. All of the 420 mg lots were within the 150 mg QR for main peak and basic variants and seven lots were within the QR for acidic variants (one lot was slightly above the QR). The charge heterogeneity is comparable between MYL-1401O 150 mg and 420 mg DP lots.*

5.1.15 Oxidation

The range of oxidation in six lots of 150 mg DP was 2.2-3.9%, and the range of oxidation in eight lots of 420 mg DP was 2.2-3.8% (Table 25 and Figure 15).

Reviewer comment: *All 150 mg lots were within the 420 mg-based QR, and all 420 mg lots were within the 150 mg QR. The levels of 420 mg and 150 mg DP oxidation are comparable.*

5.1.16 Higher order structure (DSC)

The ranges for the transition temperatures of three lots of 150 mg DP were 71.9-72.6% for Tm1 and 82.5-82.7% for Tm2, and the ranges for three lots of 420 mg DP were 70.0-72.6°C for Tm1 and 82.5-82.7% for Tm2 (Table 26 and Figure 16).

Reviewer comment: *No difference in transition temperature was observed between 150 mg DP lot BS15003580 and 420 mg DP lot BS15005600, which are derived from the same DS lots. The DSC results indicate that the tertiary structures of the 150 mg and 420 mg DP lots are comparable.*

5.1.17 Disulfide bridging (peptide map)

The masses of eight disulfide linked peptide fragments were identical between 150 mg and 420 mg DP lots and were comparable to the theoretical masses for each peptide fragment (Table 27 and Figure 17).

Reviewer comment: *The data provided demonstrate comparability of the disulfide linkages.*

Summary of the comparability assessment

Reviewer Comment: *The data show minor variability between the MYL-1401O 150 mg and 420 mg DP lots that appears to be mainly related to DS variability. The main difference observed between the 150 mg and 420 mg lots was in HER2 binding; the 420 mg lots exhibited less variability compared to the 150 mg lots. Taking the additional functional assay data into consideration, it appears more likely that the observed variability is due to the variability of the analytical method than to DP manufacturing and presentation differences.*

MYL-1401O 150 mg and MYL-1401O 420 mg DP batches are sufficiently comparable to support the inclusion of batches of both presentations in the analytical similarity assessment.

Analytical Similarity Assessment

Identification of the trastuzumab quality attributes that impact safety and efficacy

Data derived from in-house characterization studies and publically available information, were used to identify the trastuzumab quality attributes that may impact product safety and efficacy. A separate document, “Criticality Risk Ranking Document” (Section 3.2.R), details the methodology used to rank and classify the quality attributes, including risk ranking tools as described in ICH Q9. Two tools were used; the first tool (risk ranking) was used for the assessment of “product variants,” which for this purpose were designated as variants that are “due to micro-heterogeneity (including post-translational modifications such as charge variants and glycoforms),” and the second tool (Preliminary Hazard Analysis; PHA) was used for the assessment of “structural and specific functional attributes.”

Product variants were ranked based on the impact (very high, high, moderate, low, and none) that the variant may have on safety, efficacy, PK/PD and immunogenicity and on the uncertainty (very high, high, moderate, low and very low) associated with the information used to determine impact. An overall criticality/risk score (impact x uncertainty) of low, moderate, high or very high criticality was assigned to the product variants identified.

Reviewer Comment: *The criticality is based only on the calculated score, which means that attributes designated as very high risk with a moderate, low, or very low level of uncertainty are downgraded from very high criticality to high or moderate (for very low uncertainty) criticality. In addition, for example, a high-risk attribute with very low uncertainty is downgraded to low criticality. We strongly disagree with this assessment. If an attribute has been clearly or well established to have a high or very high risk, its criticality should be high/very high. This has been considered as part of the evaluation of other aspects of the analytical similarity assessment.*

The structural and functional attributes were ranked based on severity (very low, low, moderate, high, very high) of the consequences that the product attribute will have on safety, immunogenicity, and efficacy (potency and PK/PD) and the likelihood (very low/never observed, low, moderate, high, very high) that an adverse event that impacts safety and efficacy will occur if the product attribute is outside of the established acceptance range. Overall criticality scores/risk priority numbers (severity x likelihood) of low, moderate, high, or very high criticality were assigned to the product attributes.

Reviewer Comment: Using this tool, attributes designated to have very high severity were also downgraded if they had low or very low likelihood, and there is no justification provided for this assessment.

Table 4 (Table 27 of the Criticality Risk Ranking document), not reproduced here, summarizes the quality attributes and corresponding criticality risk ranks determined using the risk assessment tools.

Statistical tier assignment of the analytical methods used to assess the identified quality attributes

The risk ranking of the trastuzumab quality attributes were, in part, used to assign the corresponding analytical methods to statistical tiers for the analytical similarity assessment. The approach used for the statistical analysis of the quality attributes includes the following three tiers corresponding to varying degrees of statistical rigor:

Tier 1: Equivalence test – Analytical methods used to assess the primary mechanisms of action of trastuzumab were evaluated by equivalence testing where the equivalence margin was calculated using the equation below and was based on 1.5 times the SD of the reference product lots. For the comparator product, if the 90% two-sided confidence interval of the mean difference was within the defined equivalence margin, the attribute was determined to be analytically similar.

$$(\bar{X}_B - \bar{X}_R) \pm t_{1-\alpha, df^*} \times \sqrt{S_B^2 / n_B + S_R^2 / n_R^*}$$

Tier 2: Quality ranges – Analytical methods with variability of >15% used to assess quality attributes with very high criticality scores were evaluated using quality ranges (QR) based on the variability of the reference product, expressed as the mean $\pm$ 2 SD. Attributes assessed by a method with variability of <15% and categorized as high, moderate or low criticality were evaluated against a QR based on the mean $\pm$ 3SD of the reference product. The acceptance criterion to determine that an attribute was analytically similar was based on 90% of the lots tested falling within the QR.

Tier 3: Comparison of graphical representations and data tables – Quality attributes assessed using analytical methods not amenable to statistical analysis are assigned to Tier 3. Raw data and scatter plot distributions were provided for Tier 3 analysis.

The criticality risk ranking of the identified trastuzumab quality attributes and the corresponding analytical method tier assignments is provided in Table 5 (below; Table 28 of the Criticality Risk Ranking document).

Table 5: Risk Ranking of Quality Attributes and Tier Assignments of the Corresponding Analytical Methods

Quality Attribute	Risk Rank	Methods/tests	Tier	
Protein content	High	Ultra-violet 280 Absorption	2	
Amino acid sequence	Very High	Peptide Mapping	3	
		Intact Mass and LC/HC Mass	3	
Conformation (Secondary and Higher order structure)	Very High	Far UV Circular Dichroism	2	
		Fourier transform infrared spectroscopy	3	
		Free Cysteine	3	
		Disulfide Bridging	3	
		Near UV Circular Dichroism	3	
		Differential scanning calorimetry	3	
		Intrinsic Fluorescence	3	
		Hydrophobic Interaction Chromatography	3	
		Sub-visible Particles	Very High	MFI
Aggregates	High	Size Exclusion Chromatography - UV	2	
		Analytical Ultra Centrifugation (AUC)	3	
		Size Exclusion Chromatography – MALS	3	
Fragments	Moderate	CE-SDS (Non-Reduced)	2	
Glycoform variants	Non-glycosylated	High	CE-SDS (Reduced)	2
	Afucosylated	High	Normal Phase HPLC linked with LCMS	2
	High Mannose	High	Normal Phase HPLC	2
	Terminal Galactose	Low	Normal Phase HPLC	2
	Terminal Sialic acid	Moderate	Reverse Phase HPLC	2
Glycation	Low	Boronate affinity Chromatography	3	
Methionine Oxidation	Low	Reverse Phase HPLC	3	
Deamidation	Low	Ion Exchange HPLC, cIEF	3	
Isomerization	High	Ion Exchange HPLC, cIEF	2	
C-terminal lysine	Low	Ion Exchange HPLC, cIEF	3	

HER-2 Binding	Very High	SK-BR3 based binding assay	1
Inhibition of Proliferation	Very High	SK-BR3 cell based assay	1
ADCC	Very High	SK-BR3 and PBMC based ADCC assay	1
FcγRIIIa	Very High	FcγRIIIa Binding (b) (4) based assay	2
FcRn	High	FcRn Binding (b) (4) based assay	2
Other effector/ Fc functions	Low	FcγRIa binding (b) (4) based assay	3
	Low	FcγRIIa binding (b) (4) based assay	3
	Low	FcγRIIb binding (b) (4) based assay	3
	Low	FcγRIIIb binding (b) (4) based assay	3
	Low	C1q binding ELISA assay	3

Abbreviations: ADCC=antibody-dependent cell-mediated cytotoxicity; DLS=dynamic light scattering; ELISA=enzyme-linked immunosorbent assay; FcRn=neonatal Fc receptor; HPLC=high-performance liquid chromatography

Reviewer comment: *The methods proposed for the assessment of analytical similarity among MYL-1401O, US-Herceptin and EU-Herceptin are acceptable. Methionine oxidation and deamidation were categorized as low criticality and placed into Tier 3, although these attributes are major degradation products of trastuzumab and have been shown to impact antigen-receptor binding; deamidation can be partially evaluated through the use of the charge-based assays that are included in Tier 2 for the purpose of evaluating isomerization, and these attributes will be evaluated with respect to their potential impact to efficacy (see detailed discussion below on charge variants). Complement-dependent cytotoxicity (CDC) activity, while not included as a quality attribute in Table 5, was studied as part of the analytical similarity assessment and will be discussed below.*

Samples used in the analytical similarity assessment

The analytical similarity assessment included:

- Twenty-eight lots of US-Herceptin with labeled expiration dates between June 2013 and April 2019 (presumed lot age range of 5-48 months, all used within the shelf-life). US-Herceptin lot 516558 was used in the three-way (MYL-1401O, US-Herceptin and EU-Herceptin) comparator PK, safety and immunogenicity study, MYL-HER-1002.
- Thirty-eight lots of EU-Herceptin with labeled expiration dates between July 2013 and May 2019 (presumed lot age range of 5-48 months). EU-Herceptin lot H4078B02 was used in the clinical study MYL-HER-1002, and lots H4544H03, H4578H01 and H4561H01 were used in the two-way comparator (MYL-1401O and EU-Herceptin) efficacy and safety clinical study, MYL-HER-3001.
- Sixteen lots of MYL-1401O DP, inclusive of 150 mg and 420 mg DP lots, manufactured from November 2011 to December 2015 (lot age range from 1-43 months). The lots included in the similarity assessment were manufactured using the clinical (Process B) and commercial manufacturing (Process C) processes. According to Table 30 (below), the

following MYL-1401O 150 mg DP lots were included in clinical study MYL-HER-3001: DBBMPTV12-0003 (also included in study MYL-HER-1002), DBBMPTV12-0005, BS1400667, BS14007346, and BS14012746.

Table 30: Details of MYL-1401O DP Lots Used for Analytical Similarity Assessment

MYL-1401O presentation	Drug substance Batch number	Drug product Batch number	Manufacturing date	Purpose for which the batch was taken
MYL-1401O-150mg	DB-P02-F11F02-005	DEVBV11-0007	Nov/11	Supporting Stability data for Phase III - IMPD
	DB-P02-F11F02-006	DEVBV11-0008	Nov/11	Supporting Stability data for Phase III - IMPD
	DB-P02-F11F02-007	DBBMPTV11-0001	Dec/11	Supporting Stability data for Phase III - IMPD
	DB-P02-F11F02-008	DBBMPTV12-0001	Apr/12	Reference standard batch
	DB-P02-F12F02-001	DBBMPTV12-0003	Jul/12	Phase I batch (MYL-Her-1002); Phase III clinical batch (MYL-Her-3001)
	DB-P02-F12F02-002	DBBMPTV12-0005	Oct/12	Phase III clinical batch (MYL-Her-3001)
	DB-P02-F12F02-002	BS14006677	Jul/14	Phase III clinical batch (MYL-Her-3001)
	DB-P02-F12F02-003	BS14007346	Aug/14	Phase III clinical batch (MYL-Her-3001)
	BS14011367	BS14012746	Mar/15	Phase III clinical batch (MYL-Her-3001)
	BS15000304	BS15003340	Aug/15	Process validation Batch
MYL-1401O-440mg	BS15000673	BS15005600	Nov/15	Process validation Batch
	BS15002083	BS15005677	Nov/15	Process validation Batch
	BS15004184	BS15006002	Dec/15	Post-process validation batch
	BS15004444	BS15006421	Dec/15	Post-process validation batch

*: Data from BS14006677 has been used for Tier 1 and Tier 2 techniques. DBBMPTV12-0005 has been used for some Tier-3 techniques only

Reviewer comment: MYL-1401O DP lots manufactured using DS processes B or C (both at the ^{(b) (4)} L scale; see Section 3.2.S.2.6 for comparability assessment) and lots used in various clinical studies were included in the similarity assessment. The US-Herceptin and EU-Herceptin lots selected for the analytical similarity assessment span the assumed product shelf-life to capture innovator product differences over time.

Lot Selection

The number of lots included for the analysis of each quality attribute was based on tier assignment, criticality ranking, availability of material at the time of analysis, method variability, orthogonal approaches, shelf-life coverage, and number of lots amenable to the specific analytical method. The following table summarizes the number of US-Herceptin, EU-Herceptin, and MYL-1401O lots selected based on the tier assignment.

Table 31 Number of lots based on tier and criticality of the attribute

Tier	US-licensed Herceptin	EU-approved Herceptin	MYL-1401O lots
Tier -1	Not less than 20 lots	Not less than 20 lots	Not less than 10 lots (six 150 mg and four 440 mg lots)
Tier -2	Not less than 10 lots	Not less than 10 lots	Not less than 6 lots (three 150 mg and three 440 mg lots)
Tier -3	Not less than 3 lots	Not less than 3 lots	Not less than 4 (two 150 mg and two 440 mg)

Reviewer comment: The method used for lot number selection appears acceptable. Throughout the analytical similarity assessment, various lots and different numbers of MYL-1401O, US-Herceptin and EU-Herceptin lots were included for attribute analysis. Mylan stated that certain

lots were excluded from potency analyses due to use of different IRS at the time of analysis. In response to the IR dated March 27, 2017, historical functional data for MYL-1401O (b) (4) L DP, US-Herceptin and EU-Herceptin lots generated using various IRS were provided (Section 3.2.R Annexure 2 and 3); due to the difference in IRS, these data were not included in the similarity assessment. All functional data included in the analytical similarity assessment were those generated against the current IRS, QC/Q8/LS/001/03. However, all potency data were evaluated to the extent possible (e.g., through the use of “correction factors” based on the comparison of IRS) to ensure that the exclusion of results did not significantly impact the conclusions regarding analytical similarity. All other data obtained for the relevant lots were included in the similarity assessment. During the pre-approval inspection, the laboratories, methods, results, and analyses were further evaluated, and Mylan explained that the lot selection plan was based on the following criteria: 1) use of a common reference standard across multiple assays, 2) differing number of replicates across techniques, 3) use of data from a qualified analytical method, and 4) sample availability and testing within the assumed product shelf-life. The approach taken for lot selection is acceptable.

As previously discussed, MYL-1401O DP batches BS15003694 and BS15005879 were manufactured from the combination of two DS lots. The individual DS lots were also used to manufacture three additional individual DP lots. An IR was sent to Mylan requesting that MYL-1401O DP lots BS15003694 and BS15005879 be excluded from the analytical similarity assessment, because the majority of the variability of the critical attributes is derived from DS manufacturing.

(b) (4) was the primary location of analysis for the similarity assessment; however, the assessments of FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, and higher order structure by differential scanning calorimetry were conducted at Mylan Pharmaceuticals Private Limited (Hyderabad, India), and the assessment of aggregates by analytical ultracentrifugation was done at (b) (4).

Formulation

MYL-1401O DP is formulated with sorbitol and PEG 3350, while US-Herceptin and EU-Herceptin are formulated with polysorbate 20 and trehalose. The following table provides a comparative description of the MYL-1401O, US-Herceptin and EU-Herceptin formulations.

Reviewer Comment: An additional version of Mylan trastuzumab is (b) (4) as US- and EU-Herceptin, and this formulation was included in the method validation studies. Between the inclusion of both formulations in method validation and the dilutions of the samples in many methods, it is expected that the different formulations will not impact the analytical testing results.

	MYL-1401O (mg/vial)		US-Herceptin (mg/vial)	EU-trastuzumab (mg/vial)
Drug Substance	150	440	440	150
Trehalose	(b) (4)	----	400	136.2
Polysorbate 20		----	1.8	0.6
Sorbitol		(b) (4)	----	----
PEG-3350/Macrogol 3350			----	----
L-Histidine			6.4	2.16
L-Histidine HCl			9.9	3.36

Table prepared by CMC reviewer

Results of Analytical Similarity Assessment

Biological and Functional Assays Representing Mechanism of Action

6.1.3.1 HER2 binding – Tier 1

Twenty-two lots of US-Herceptin, 22 lots of EU-Herceptin, and 9 lots of MYL-1401O DP were evaluated for HER2 binding activity using flow cytometry. The representative dose response curves of US-Herceptin, EU-Herceptin, and MYL-1401O appear similar when overlaid against the IRS curve. The HER2 binding ranges for the three products shown in the scatter plot below are: US-licensed Herceptin – 0.65-1.25, EU-approved trastuzumab – 0.84-1.20, and MYL-1401O – 0.85-1.07 (Figure 19). The relative potency values for MYL-1401O lots are within the ranges of both the US-Herceptin and EU-Herceptin lots. The US-Herceptin range is wider than the MYL-1401O and EU-Herceptin ranges due to lots 3001143 (relative potency = 0.65) and 3001168 (relative potency = 1.25), with expiry dates of October 2018 and September 2018, respectively. Equivalence testing shows that the 2-sided confidence interval (CI) of the MYL-1401O relative potency mean differences are within the equivalence margin for both the US-Herceptin and EU-Herceptin lots and that the EU-Herceptin CI of the mean differences is within the US-Herceptin margin (Figure 20, below).

Figure 19: Scatter Plot Distribution of Relative HER2 Binding of MYL-1401O, US-Licensed Herceptin, and EU-Approved Herceptin

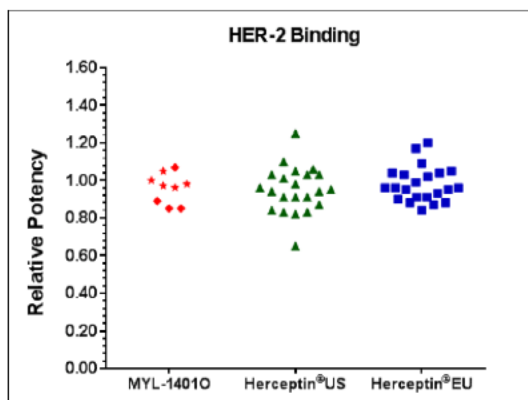
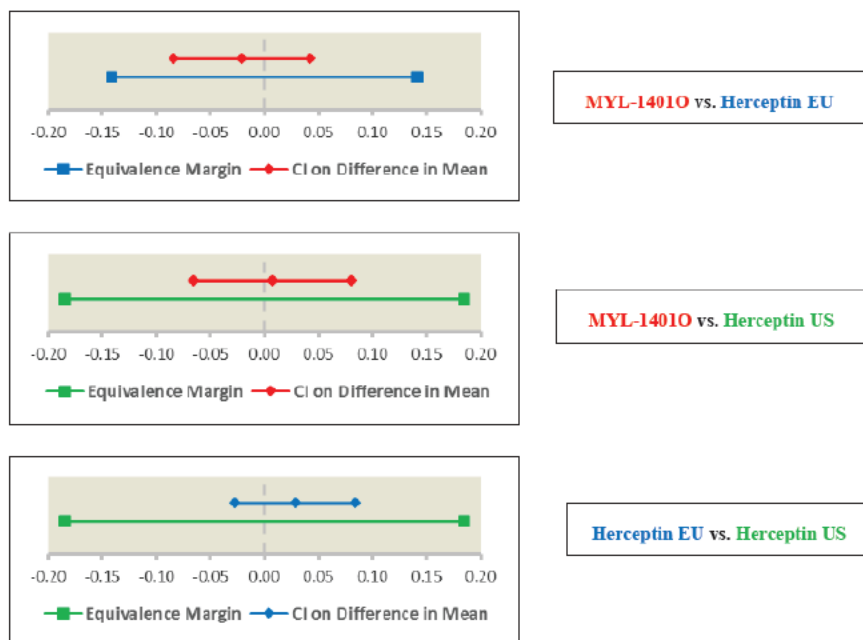


Figure 20: Graphical Plots for Equivalence Test of Relative HER2 Binding



Reviewer comment: The evaluation of HER2 binding supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among US-Herceptin, MYL-1401O, and EU-Herceptin.

6.1.3.2 Inhibition of Proliferation – Tier 1

Twenty-two lots of US-Herceptin, 22 lots of EU-Herceptin, and 9 lots of MYL-1401O DP were evaluated for inhibition of proliferation using the previously described SKBR3 cell-based assay. The US-Herceptin and EU-Herceptin lots included in the analysis were no less than 8 months old at the time of analysis (based on a hypothesized expiry period of 48 months), while the MYL-1401O lots spanned an age range of 1-42 months. The representative dose response curves provided for each drug product appear similar to the IRS used as a comparator. The relative potency value ranges for each product depicted in the scatter plots below are: US-licensed Herceptin – 0.92-1.26, EU-approved trastuzumab – 0.90-1.28, and MYL-1401O – 0.94-1.24 (Figure 22). The equivalence testing results show that the CI of the difference in the mean of the MYL-1401O lots are within the equivalence margin of US-Herceptin and EU-Herceptin. The CI of the difference of the means of the EU-Herceptin lots is within the EAC of the US-Herceptin lots (Figure 23, below).

Figure 22: Scatter Plot Distribution of Relative Potency of MYL-14010, US-Licensed Herceptin, and EU-Approved Herceptin

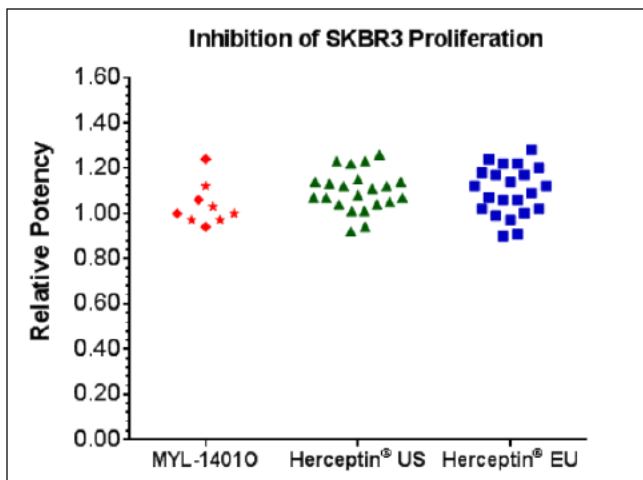
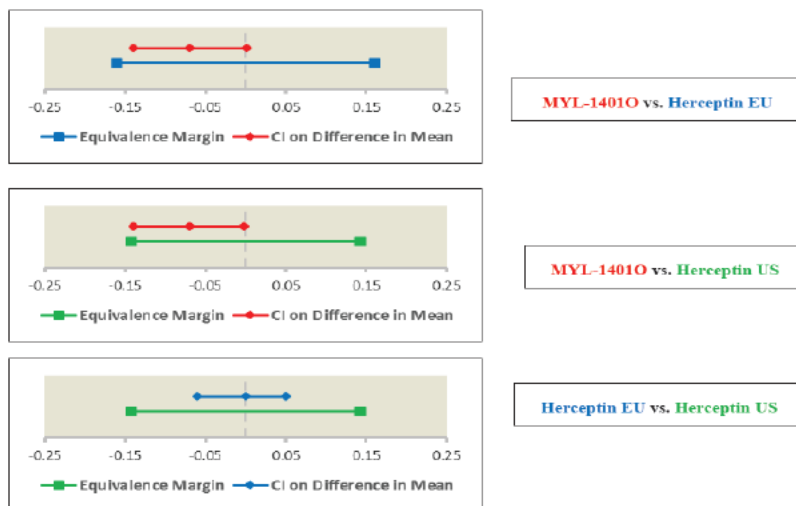


Figure 23: Graphical Plots for Equivalence Test of Relative Potency



Reviewer comment: The lower end of the CI of the MYL-14010 lots is very close to the lower end of the US-Herceptin and the EU-Herceptin-based equivalence margin. However, the overall statistical evaluation supports that the MYL-14010 lots are statistically equivalent to both the US- and EU-Herceptin lots. The evaluation of the inhibition of proliferation supports a demonstration of highly similar between MYL-14010 and US-Herceptin and establishment of analytical bridges among MYL-14010, US-Herceptin, and EU-Herceptin.

6.1.3.3 ADCC activity – Tier 1

ADCC activity was evaluated for 21 lots of US-Herceptin, 26 lots of EU-Herceptin and 13 lots of MYL-14010 DP using the previously described SKBR3 cell based assay. The representative dose response curves provided for each drug product appear similar to the IRS used as a comparator. The ranges for the relative ADCC activity depicted in the scatter plot below are: US-Herceptin – 0.64-1.13, EU- trastuzumab – 0.62-1.31, and MYL-14010 – 0.73-1.18 (Figure

25). The CI of the difference of the mean of the MYL-1401O DP lots are within the EAC of both the US-Herceptin lots and the EU-Herceptin lots (Figure 26, below). The CI of the difference of the mean of the EU-Herceptin lots is within the EAC of the US-Herceptin lots.

Figure 25: Scatter Plot Distribution of the Relative ADCC Activity for MYL-1401O, US-Licensed Herceptin, and EU-Approved Herceptin

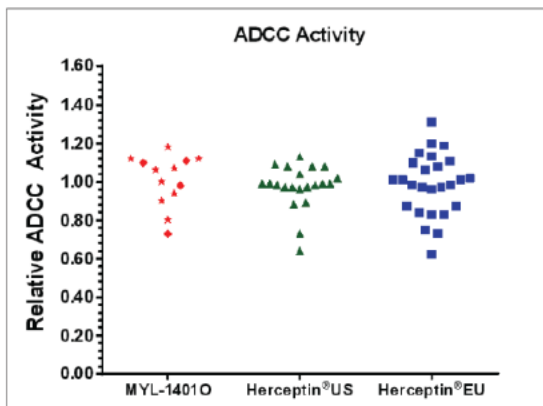
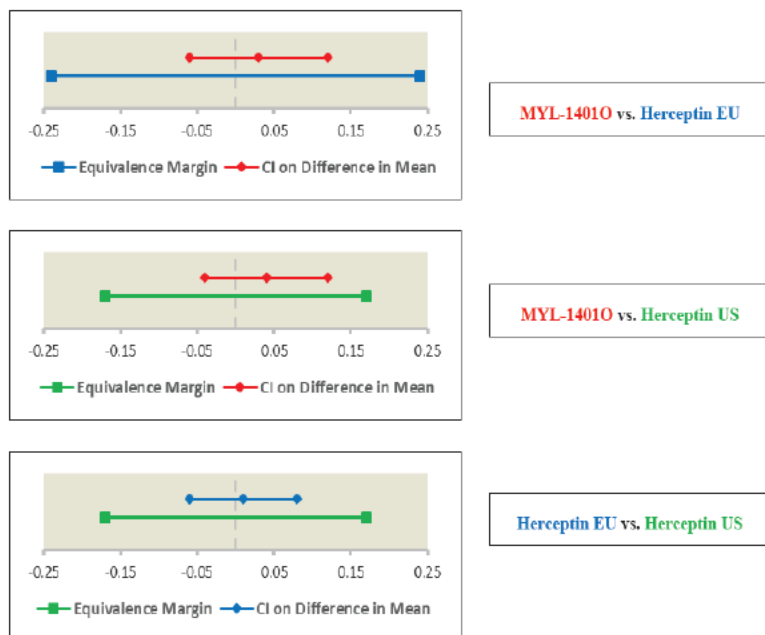


Figure 26: Graphical Plots for Equivalence Test of Relative ADCC Activity



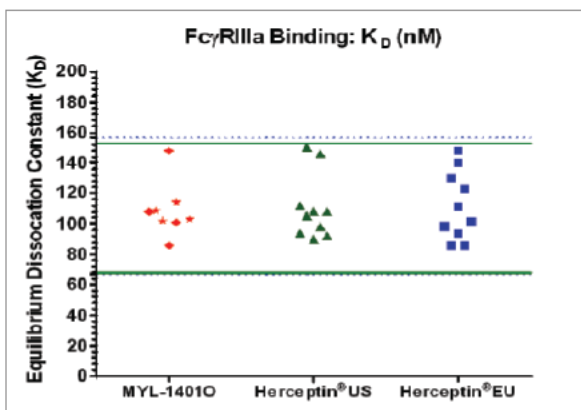
Reviewer comment: Overall, the evaluation of ADCC activity supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.3.4 FcγRIIIa (V₁₅₈) Binding – Tier 2

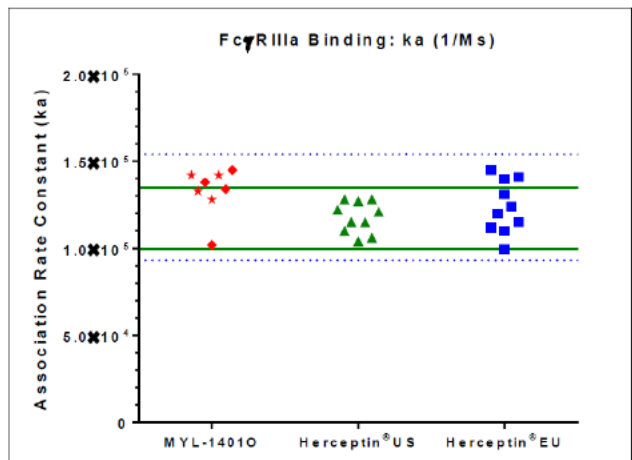
The binding affinities of 10 lots of US-Herceptin, 10 lots of EU-Herceptin, and 8 lots of MYL-1401O DP to the high affinity FcγRIIIa isoform, V₁₅₈, were evaluated using SPR and Tier 2 statistical analyses. The binding kinetics were reported as k_a , k_d , and k_D ($k_D = k_a:k_d$). The average k_a (1/Ms) ranges were: US-Herceptin – 1.04×10^5 - 1.28×10^5 , EU-Herceptin – 9.95×10^4 -

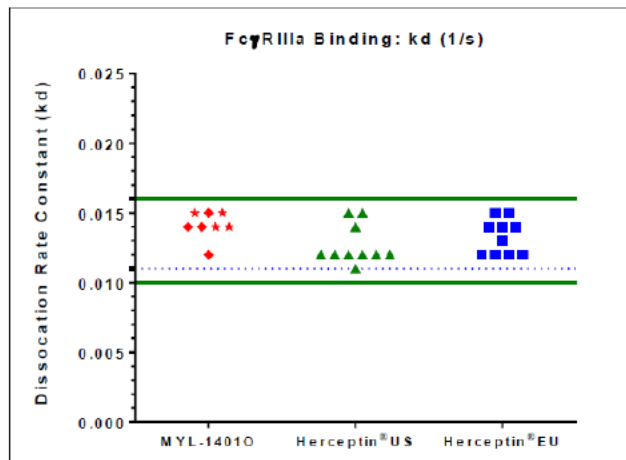
1.45x10⁵, and MYL-1401O – 1.02x10⁵-1.45x10⁵. The average k_d (1/s) ranges were: US-Herceptin- 0.011-0.015, EU-Herceptin - 0.012-0.015, and MYL-1401O – 0.012-0.015. The average k_D (nM) ranges were: US-Herceptin – 90-150, EU-Herceptin – 86-148, and MYL-1401O – 86-148. The scatter plots (below) show that 4 of the 8 MYL-1401O lots and 4 of the 10 lots of the EU-Herceptin were outside of the US-Herceptin QR for k_a (QR = 9.96X10⁴-1.35X10⁵, based on ±2 SD). All of the MYL-1401O and EU-Herceptin lots were within the US-Herceptin k_d QR (0.010-0.016) and k_D QR (68-153). All MYL-1401O and US-Herceptin lots were within the EU-Herceptin QRs (k_a QR = 9.32X10⁴-1.54X10⁵; k_d QR = 0.011-0.016; k_D QR = 67-157).

Figure 27: Scatter Plot Distribution of FcγRIIIa-V138 Kinetic Rate Constants and Affinity Constant for MYL-1401O, US-Licensed Herceptin, and EU-Approved Herceptin



Solid Green lines represents the Quality Range (Mean±2SD) established for US-licensed Herceptin
 Dotted Blue lines represents the Quality Range (Mean±2SD) established for EU-approved Herceptin



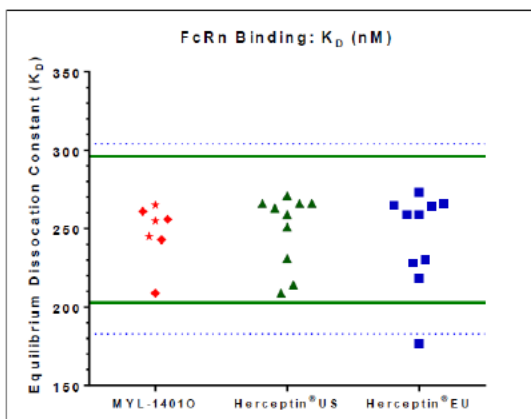


Reviewer comment: The MYL-1401O DP lots had slightly higher k_a values compared to the US-Herceptin and some of the EU-Herceptin lots, and while this difference was observed, it appears that overall binding to Fc γ RIIIa is similar (with similar internal variability) based on consistent k_a and k_D values. In addition, due to assay variability, the QR was based on $\pm 2SD$, but if the QR were based on $\pm 3SD$, the MYL-1401O lots would all be within the US-Herceptin QR. The k_D of an antibody provides a measurement of the interaction rates between the antibody and the antigen by taking into consideration both the rate of dissociation and the rate of association. The k_D values are similar among the three products, with a similar proportion of MYL-1401O, US-Herceptin and EU-Herceptin lots showing stronger binding affinities, and only a few lots of each product exhibiting lower affinities. The magnitude of the differences, combined with the expected assay variability, is not great enough to indicate a potential for clinical impact. Considering the overall consistency shown in the k_D values among the three products, the data support a demonstration of highly similar between MYL-1401O and US-Herceptin and establishment of the analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

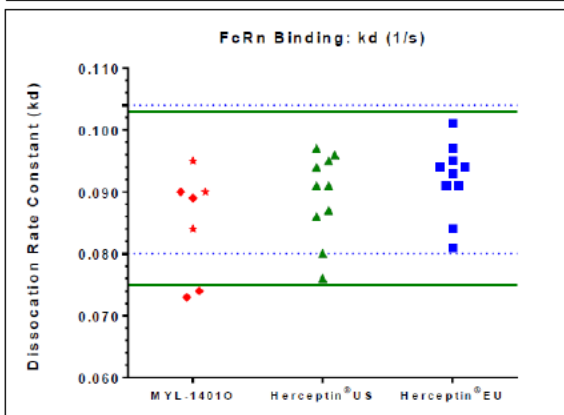
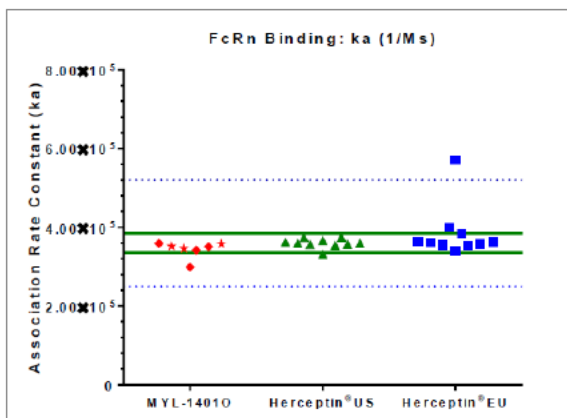
6.1.3.5 FcRn binding – Tier 2

FcRn binding kinetics (SPR) were determined for 10 lots of US-Herceptin, 10 lots of EU-Herceptin, and 7 lots of MYL-1401O DP and evaluated by Tier 2 statistical analyses. The average k_a (1/Ms) ranges were: US-Herceptin – 3.31×10^5 - 3.75×10^5 , EU-Herceptin – 3.40×10^5 - 5.72×10^5 , and MYL-1401O – 2.99×10^5 - 3.59×10^5 . The average k_d (1/s) value ranges were: US-Herceptin – 0.076-0.097, EU-Herceptin – 0.081-0.101 and MYL-1401O – 0.073-0.095. The average k_D (nM) ranges were: US-Herceptin – 208-271, EU-Herceptin – 177-273, and MYL-1401O – 209-265. The scatter plots show that one lot of MYL-1401O and three lots of EU-Herceptin were outside the US-Herceptin QR for k_a (3.35×10^4 - 3.84×10^5); two MYL-1401O lots and two EU-Herceptin lots were outside the US-Herceptin QR for k_d (0.075-0.103); and one EU-Herceptin lot was outside the US-Herceptin QR for k_D (203-296) (Figure 28, below). For k_a and k_D , all MYL-1401O and US-Herceptin lots were within the EU-Herceptin QR, and for k_a , two MYL-1401O lots and one US-Herceptin lot were outside the EU-Herceptin QR.

Figure 28: Scatter Plot Distribution of FcRn Kinetic Rate Constants and Affinity Constant for MYL-14010, US-Licensed Herceptin, and EU-Approved Herceptin



Solid Green lines represents the Quality Range (Mean±2SD) established for US-licensed Herceptin
 Dotted Blue lines represents the Quality Range (Mean±2SD) established for EU-approved Herceptin



Reviewer comment: A single EU-Herceptin lot (H4578H01) was below its own QR and the US-Herceptin QR for k_D and above the two QRs for k_a . The k_D values suggest that this lot has stronger affinity to FcRn than the other lots, which may result in faster antibody clearance and a potential impact on PK. However, this EU-Herceptin lot was included clinical study MYL-HER-3001, where no differences clinically meaningful differences were observed in PK. Two out of 7 MYL-14010 420 mg PV lots had k_a values below the US-Herceptin QR; however, the k_a and k_D

values reported for these two lots were not significantly different than the other MYL-1401O, US-Herceptin or EU-Herceptin lots. Overall similar $Fc\gamma Rn$ k_a , k_d and k_D binding affinities were shown among US-Herceptin, EU-Herceptin and MYL-1401O, with similar variability also shown within the individual product lots. The magnitude of the differences, combined with the expected assay variability, is not great enough to indicate a potential for clinical impact. The data support a demonstration of highly similar between MYL-1401O and US-Herceptin and establishment of the analytical bridges between MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.3.6 Fc γ RIa binding- Tier 3

Fc γ RIa binding kinetics were assessed by SPR and analyzed as a Tier 3 quality attribute for four US-Herceptin lots, five EU-Herceptin lots, and seven MYL-1401O DP lots (Figure 29). US-Herceptin and EU-Herceptin limits were based on ± 3 SD. The following are the ranges for:

- US-Herceptin: k_a : 3.33×10^5 - 4.62×10^5 1/Ms; k_d : 6.90×10^4 - 8.42×10^4 1/s; k_D : 1.74-2.54 nM
- EU-Herceptin: k_a : 3.73×10^5 - 4.22×10^5 1/Ms; k_d : 6.97×10^4 - 7.58×10^4 1/s; k_D : 1.67-2.04 nM
- MYL-1401O: k_a : 4.02×10^5 - 4.34×10^5 1/Ms; k_d : 7.01×10^4 - 7.72×10^4 1/s; k_D : 1.63-1.81 nM.

The data show similar ranges for US-Herceptin, EU-Herceptin and MYL-1401O lots, although the MYL-1401O lots appear to have less variability than the US-Herceptin and EU-Herceptin lots. All lots are within the limits.

Reviewer comment: *The numbers of lots included in the Fc γ RIa binding assessment are limited, but are generally acceptable for Tier 3 analysis. Although QR are not part of the acceptance criteria for the Tier 3 attributes, the limits provide a reasonable mechanism for evaluating the similarity of the results. The variability observed in the US-Herceptin lots may be due to SPR assay variability or inherent manufacturing variability. Overall, the binding kinetic ranges are similar and the evaluation of the Fc γ RIa binding kinetics is acceptable. The data support a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.3.7 Fc γ RIIa-R₁₃₁ binding – Tier 3

Fc γ RIIa-R₁₃₁ binding kinetics were assessed by SPR and analyzed as a Tier 3 quality attribute for four US-Herceptin lots, five EU-Herceptin lots, and seven MYL-1401O DP lots (Figure 30).

US-Herceptin and EU-Herceptin limits were based on ± 3 SD. The following are the ranges for:

- US-Herceptin: k_a : 9.52×10^4 - 1.28×10^5 1/Ms; k_d : 0.55-0.64 1/s; k_D : 5.05-5.95 nM
- EU-Herceptin: k_a : 8.75×10^4 - 1.30×10^5 1/Ms; k_d : 0.55-0.64 1/s; k_D : 4.95-6.34 nM
- MYL-1401O DP: k_a : 1.12×10^5 - 1.21×10^5 1/Ms; k_d : 0.58-0.62 1/s; k_D : 5.04-5.43 nM

The data show similar ranges for US-Herceptin, EU-Herceptin and MYL-1401O lots, although, similar to the binding kinetics of Fc γ RIa, the MYL-1401O lots appear to have less variability than the US-Herceptin and EU-Herceptin lots. All lots were within the limits.

Reviewer comment: *The variability observed in the US-Herceptin and EU-Herceptin lots may be due to assay or manufacturing variability. The data support a demonstration of highly*

similar among MYL-1401O and US-Herceptin and establishment of the three-way analytical bridge.

6.1.3.8 FcγRIIb/c binding – Tier 3

FcγRIIb/c binding kinetics were assessed by SPR and analyzed as a Tier 3 quality attribute for four US-Herceptin lots, five EU-Herceptin lots, and seven MYL-1401O DP lots (Figure 31). US-Herceptin and EU-Herceptin limits were based on ± 3 SD. The following are the ranges for:

- US-Herceptin: k_a : 1.04×10^5 - 1.19×10^5 1/Ms; k_d : 0.97-1.03 1/s; k_D : 8.19-9.81 nM
- EU-Herceptin: k_a : 1.00×10^5 - 1.07×10^5 1/Ms; k_d : 0.97-1.01 1/s; k_D : 9.10-9.92 nM
- MYL-1401O DP: k_a : 9.33×10^4 - 1.07×10^5 1/Ms; k_d : 0.92-0.96 1/s; k_D : 8.98-9.89 nM

The data show similar ranges in the FcγRIIb/c binding kinetics for US-Herceptin, EU-Herceptin and MYL-1401O lots. One lot of MYL-1401O was just outside the US- and EU-Herceptin limit for k_d .

Reviewer comment: *The overall evaluation of the binding kinetics supports a demonstration of highly similar between MYL-1401O and US-Herceptin and establishment of the analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.3.9 FcγRIIIb binding – Tier 3

FcγRIIIb binding kinetics were assessed by SPR and analyzed as a Tier 3 quality attribute for four US-Herceptin lots, five EU-Herceptin lots, and seven MYL-1401O DP lots (Figure 32). US-Herceptin and EU-Herceptin limits were based on ± 3 SD. The following are the ranges for:

- US-Herceptin: k_a : 5.19×10^4 - 5.62×10^4 1/Ms; k_d : 0.19-0.28 1/s; k_D : 3.54-5.35 nM
- EU-Herceptin: k_a : 5.10×10^4 - 5.38×10^4 1/Ms; k_d : 0.19-0.28 1/s; k_D : 3.58-5.46 nM
- MYL-1401O DP: k_a : 5.49×10^4 - 6.27×10^4 1/Ms; k_d : 0.20-0.24 1/s; k_D : 3.54-4.27 nM

The data show similar ranges in the FcγRIIIb binding kinetics for US-Herceptin, EU-Herceptin and MYL-1401O lots. One lot of MYL-1401O was slightly outside the US-Herceptin limit for k_a , and two lots were outside the EU-Herceptin limit.

Reviewer comment: *The overall evaluation of the FcγRIIIb binding kinetics supports a demonstration of highly similar between MYL-1401O and US-Herceptin and establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.3.10 C1q binding – Tier 3

C1q binding is a critical component of Fc-mediated complement-dependent cytotoxicity (CDC) and was evaluated using ELISA as a Tier 3 quality attribute. US-Herceptin and EU-Herceptin limits were based on ± 3 SD. The average relative binding ranges were 0.76-0.96 for four lots of US-Herceptin, 0.64-1.04 for five lots of EU-Herceptin, and 0.89-1.02 for seven lots of MYL-1401O. All lots were within the limits.

Reviewer comment: The C1q data show similar binding affinities among the three products. The data support a demonstration of highly similar for US-Herceptin and MYL-1401O and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.3.11 CDC assay – single assessment

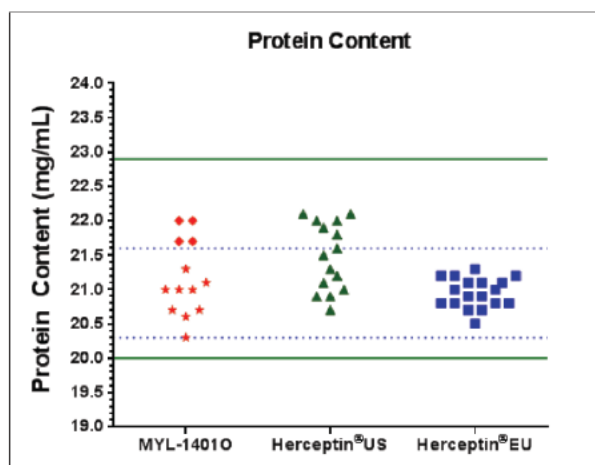
CDC activity was investigated as a one-time assessment using one lot of each of US-Herceptin, EU-Herceptin, MYL-1401O 150 mg DP, and MYL-1401O 420 mg DP. HER2 overexpressing SKBR3 cells were used the target cell line and were treated with increasing concentrations of antibody with or without undiluted (Figure 34) or 10-fold diluted (Figure 35) human plasma.

Reviewer comment: The results show no differences in CDC activity among MYL-1401O (150 mg or 420 mg), US-Herceptin, and EU-Herceptin in the presence of neat or diluted plasma. The data support a demonstration of highly similar for US-Herceptin and MYL-1401O and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.4 Protein content – Tier 2

Protein content was determined using UV₂₈₀ and the extinction coefficient of 1.48 for trastuzumab (see discussion on the adequacy of the extinction coefficient determination in Section 3.2.S.3.1.3.1). Data from 15 lots of US-Herceptin, 18 lots of EU-Herceptin, and 15 lots of MYL-1401O DP were analyzed using QRs based on the mean $\pm$ 3 times the SD of the reference product lots (Figure 36, below). The protein content ranges were: US-Herceptin – 20.7-22.1 mg/ml, EU-Herceptin – 20.5-21.3 mg/ml, and MYL-1401O – 20.3-22.0 mg/mg. All MYL-1401O and EU-Herceptin lots were within the US-Herceptin QR. However, only 69% of MYL-1401O lots (all MYL-1401O 150 mg lots) and 60% of US-Herceptin lots were within the EU-Herceptin QR.

Figure 36: Scatter Plot of Protein Content in MYL-1401O, US-Licensed Herceptin, and EU-Approved Herceptin



Solid Green lines represents the Quality Range (Mean $\pm$ 3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean $\pm$ 3SD) established for EU-approved Herceptin

Reviewer comment: As discussed previously and shown in Figure 36, MYL-1401O 420 mg (21.7-22.1 mg/ml) DP lots appear to have slightly higher protein concentration than the 150 mg

lots (20.3-21.3 mg/ml), which is likely due to differences in the DP filling aspect of the manufacturing processes used to produce the 150 mg and 420 mg lots. To be consistent with both 420 mg US-Herceptin and 150 mg EU-Herceptin, the MYL-1401O DP manufacturing process was designed to match the protein content of each, within reasonable manufacturing tolerances. The above data confirm that the reconstituted protein concentrations in the MYL-1401O vials are similar to those of the US-Herceptin vials. Additionally, the data show similarity between the protein concentrations of the MYL-1401O 150 lots used in the clinical studies and the EU-Herceptin lots. Overall, the data show similar ranges of protein concentration between US-Herceptin and MYL-1401O, therefore supporting a demonstration of highly similar between the two products. All of the 150 mg MYL-1401O lots are consistent with the EU-Herceptin lots. Moreover, all of the lots evaluated for each of the three products have protein concentrations that are within an acceptable range of the target concentration. Therefore, the protein content analysis also supports establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

Assessment of product-related impurities

6.1.5.1 HMWS by SEC-HPLC – Tier 2

SEC-HPLC was used to analyze size variants for 26 lots of US-Herceptin, 38 lots of EU-Herceptin, and 13 lots of MYL-1401O. Representative chromatogram overlays show minor differences in HMWS content among all three products. The ranges for HMWS and monomer are: US-Herceptin – 0.17-0.74% HMWS, 99.2-99.7% monomer; EU-Herceptin - 0.27-0.78% HMWS, 99.2-99.7% monomer; and MYL-1401O - 0.19-0.42% HMWP, 99.5-99.8% monomer (Figure 38). All lots were within the US- and EU-Herceptin QRs.

Reviewer comment: *The data show marginally lower HMWS and slightly higher monomer in the MYL-1401O lots compared to the US-Herceptin and EU-Herceptin lots. The differences observed may be attributed to the age of the material at the time of analysis. The MYL-1401O range was 1-18 months, the US-Herceptin range was 5-36 months, and the EU-Herceptin range was 5-48 months. A correlation can be observed between older material and an increase in HMWS and decrease in monomer content. The overall evaluation of size variants supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.5.2 Size variants by SEC-MALS – Tier 3

The molar mass of the monomer species in 2 US-Herceptin lots, 5 EU-Herceptin lots, and 10 MYL-1401O DP lots was determined using SEC-MALS. The molecular weights were: US-Herceptin – 159.4-160.1 kDa, EU-Herceptin – 158.3-160.1 kDa, and MYL-1401O – 160.0-162.8 kDa. The molecular weights of the monomer content among the three products differ by only 1.7-2.7 kDa.

Reviewer comment: *The overall of monomer molar masses support a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.5.3 Analytical Ultracentrifugation (AUC) – Tier 3

Aggregate formation was analyzed by sedimentation velocity using AUC as an orthogonal method to SEC-HPLC. Main peak, HMWS, dimer, species larger than dimer, and fragment data were provided for three lots of US-Herceptin, four lots of EU-Herceptin and four lots of MYL-1401O DP. The data show similar ranges of main peak content, HMWS, dimer, “larger than dimer” and fragments among the batches analyzed. As observed in the SEC-HPLC analysis, minor decreases in main peak and increases in HMWS and fragmentation appear to correlate with the age of the material at the time of analysis. The sedimentation coefficients were also similar among products.

***Reviewer comment:** The AUC analyses show similar size variants among the three products and the results are consistent with the SEC-HPLC analyses. The AUC data support a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.6.1 Fragments by CE-SDS non-reduced – Tier 2

An assessment of low molecular weight species (LMWS) was conducted using CE-SDS under non-reducing conditions. Representative electropherogram overlays show similar levels of fragmentation among two lots each of US-Herceptin, EU-Herceptin and MYL-1401O. Quantitative results for 19 lots of US-Herceptin, 26 lots of EU-Herceptin, and 12 lots of MYL-1401O DP show that the levels of each LMWS quantitated were similar among the three products. The ranges of the total fragments are: US-Herceptin- 1.34-2.69%, EU-Herceptin- 1.22-3.00%, and MYL-1401O- 1.47-2.79% (Figure 43). A correlation was shown between total fragment content and the ages at the time of analysis, specifically for the MYL-1401O lots, where the four younger 420 mg DP lots appeared to have less total fragments than the older 150 mg DP lots (Figure 43). The age correlation was also noted in several US-Herceptin (6-40 months) and EU-Herceptin lots (5-48 months). For total fragments, two EU-Herceptin lots were higher than the US-Herceptin QR. Additionally, minor differences were shown between MYL-1401O, US-Herceptin and EU-Herceptin lots with respect to the various fragment species evaluated. Specifically, for LC, two lots of MYL-1401O, one lot of US-Herceptin and one lot of EU-Herceptin were higher than the US-Herceptin QR, all lots were within the EU-Herceptin QR. For Fab/HC, one lot of MYL-1401O and one lot of EU-Herceptin was higher than the US-Herceptin QR and all lots were within the EU-Herceptin QR. For 2H, all lots were within the US-Herceptin QR, while two US-Herceptin lots were higher than the EU-Herceptin QR. For 2H1L, one lot of MYL-1401O and two lots of EU-Herceptin were higher than the US-Herceptin QR, and all lots were within the EU-Herceptin QR. For HL, one US-Herceptin lot was higher than its own QR, and all lots were within the EU-Herceptin QR.

***Reviewer comment:** Overall, there were minor differences with respect to individual LMWS evaluated; however, with the exception of the LC, these results met the expectation that 90% of the individual lots were within the QR. For the LC, one of the US-Herceptin lots was also outside its established QR. The levels of each of these variants were very low (<1% for LC and Fab/HC; <2% for 2H1L), the standard deviations are very small, and the differences are not*

expected to be clinically meaningful. The overall of assessment of fragmentation as determined by CE-SDS non-reduced supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

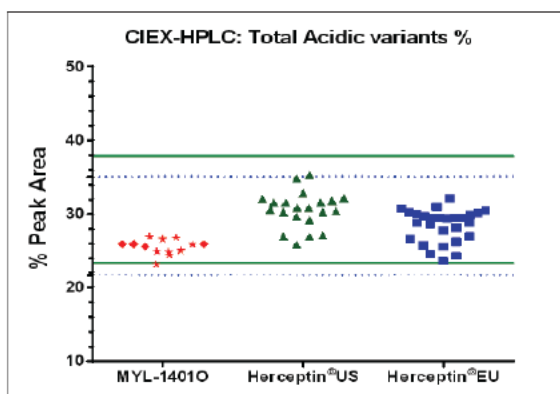
6.1.7.1 Charge variants by IEX-HPLC – Tier 2

Charge variants were assessed using IEX-HPLC and the data for acidic, main and basic species were provided for 21 lots of US-Herceptin, 27 lots of EU-Herceptin, and 13 lots of MYL-1401O (Figure 45). Representative chromatographic overlays show similar peaks among the US-Herceptin, EU-Herceptin and MYL-1401O DP lots. The following are the quantitative ranges for the identified variants:

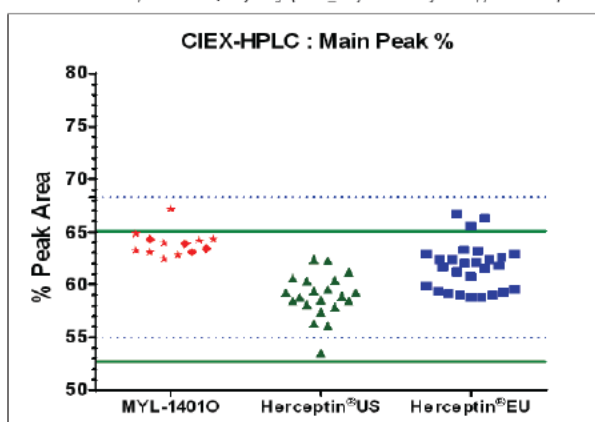
- US-Herceptin lots: acidic – 25.9-35.3%, main – 53.5-62.4%, basic – 7.2-13.7%
- EU-Herceptin lots: acidic – 24.3-32.1%, main – 58.8-66.7%, basic – 7.6-11.5%
- MYL-1401O lots: acidic – 23.2-26.9%, main – 62.5-67.2%, basic – 9.1-12.5%

MYL-1401O DP lots have a lower level of acidic variants (mean – 25.4%) compared to the US-Herceptin lots (mean – 30.6%) and the EU-Herceptin lots (mean – 28.4%), which correlates with a higher level of main peak for MYL-1401O (mean – 64.1%) compared to US-Herceptin lots (mean – 58.8%) and EU-Herceptin lots (mean – 61.7%). The three products have relatively similar levels of basic variants. The sponsor stated that the differences were potentially due to the CpB treatment included in the MYL-1401O manufacturing process to remove basic C-terminal lysine residues; however, this would lead to a difference in basic peak. While there were a few results outside the QR, the QR criteria were met for all evaluations, with the exception of the comparison of EU-Herceptin to the US-Herceptin QR for main peak, for which 89% (rather than 90%) of the lots were within the QR.

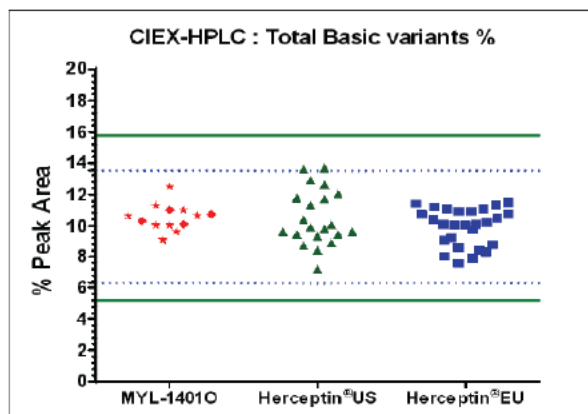
Figure 45: Scatter Plot Distribution of Total Acidic, Total Basic and Main Peak in MYL-1401O, US-Licensed Herceptin and EU-Approved Herceptin Lots



Solid Green lines represents the Quality Range ($Mean \pm 3SD$) established for US-licensed Herceptin
 Dotted Blue lines represents the Quality Range ($Mean \pm 3SD$) established for EU-approved Herceptin



Solid Green lines represents the Quality Range ($Mean \pm 3SD$) established for US-licensed Herceptin
 Dotted Blue lines represents the Quality Range ($Mean \pm 3SD$) established for EU-approved Herceptin



Solid Green lines represents the Quality Range ($Mean \pm 3SD$) established for US-licensed Herceptin
 Dotted Blue lines represents the Quality Range ($Mean \pm 3SD$) established for EU-approved Herceptin

Additional comparative characterization data were included in Section 3.2.S.3.2 (Impurities). The acidic, main and basic charge variants were isolated, enriched and analyzed for US-Herceptin batch 489766, EU-Herceptin batch H4435B01, and MYL-1401O DS batch BS15000304 (150 mg PV batch). IEX-HPLC characterization of the acidic and basic peaks identified five acidic isoforms (A4 + A5, A3, A2, A2*, A1) and four basic isoforms (B1, B1*, B2, B3) in the MYL-1401O lot. All isoforms were present in the US-Herceptin and EU-

Herceptin batches with the exception of the A2* and B1* variants. The acidic and basic variants were independently enriched and physicochemical and functional analyses were conducted.

Reviewer comment: *In the response to IR dated June 2, 2018, Mylan provided additional characterization data with respect to modification differences among the three products such as levels of oxidation, deamidation and isomerization found in the various charged peaks. In addition to the response, document 'MYL-14010 Impurity Characterization Data' was submitted to BLA Section 3.2.S.3.2. The information provided in these additional documents was incorporated in the following discussion.*

Aggregation and fragmentation analysis of fractionated charge variant peaks

SEC-HPLC

The content of HMWS, monomer, and LMWS present in each charge variant peak was evaluated by SEC-HPLC. The results for all three products show higher LMWS content in the acidic variants and higher HMWS content in the basic variants, specifically variant B3. Consistent with the main SEC-HPLC data, the HMWS content present in variant B3 of the US-Herceptin (12.7%) and EU-Herceptin (7.0%) lots are higher compared to the MYL-14010 lot (2.6%). Due to the small amount, the B1* variant was not evaluated.

CE-SDS non-reduced

Fragmentation content in each variant peak was evaluated by CE-SDS non-reduced. Chromatograms and quantitative analyses showed similar species in each peak but higher amounts of the 2H1L and 2H fragments in the acidic variants (e.g., A4+A5) of the MYL-14010 lot as compared to the US-Herceptin and EU-Herceptin lots. The A2* variant, which is present only in the MYL-14010 lot, contains mostly 2H and 2H1L fragments. The A1 variant appears enriched in the 2H fragment. Fragmentation was apparent in higher amounts in the acidic variants as compared to the basic variants.

CE-SDS reduced

The content of LC, HC, NG-HC and p75/p100 present in each charge variant peak was evaluated by CE-SDS reduced. With the exception of very minor size variants and the minor differences that were noted as part of the main similarity assessment, the contents were similar among all three products.

Degradation-related modifications present in charge peaks groups

Peptide mapping

Tryptic peptide mapping by LC-ESI-MS was used to evaluate the following site-specific modifications related to the degradation profiles of the molecules: deamidation at LC Asn 30, HC Asn 55, HC Asn 387/392, and HC Asn 318; oxidation at HC M 255, LC M4, HC M83, HC M107, HC M361, and HC M431; and C-terminal lysine. Deamidated species were present in the

acidic peak groups, oxidation was present in both acidic (to a lesser degree) and basic groups, and C-terminal lysine was present in basic peak groups. The degradation-related species were consistently present in the same charge peak groups for all three products, except for a lack of C-terminal lysine residues in MYL-1401O peak groups B1/B1* and B3.

The relative percent of each degradation-related species for three MYL-1401O batches, the MYL-1401O IRS, one US-Herceptin batch, and one EU-Herceptin batch were provided in the IR response. There was a significant amount of deamidation (up to 19.6% at Asn 30) of Asn 30, Asn 55, Asn 318, and Asn 387/392; there was slightly less deamidation in the MYL-1401O batches than in US- or EU-Herceptin. There was a lower amount of methionine oxidation (up to 4.3% at M 255) of M 255, M4, M83, and M431; there was also slightly less oxidation in MYL-1401O batches than in US-or EU-Herceptin. No oxidation of M107, in the CDR, was detected in any of the products. There were low levels of C-terminal lysine in all products; as expected based on the manufacturing process, there were slightly lower levels in MYL-1401O. There were no modifications detected in MYL-1401O lots that were not also present in US-Herceptin and EU-Herceptin lots.

Reviewer comment: *The cumulative amount of Asn deamidation was greater in US-Herceptin and EU-Herceptin lots compared to MYL-1401O; this difference is most likely the main contributor to the increased levels of overall acidic variants present in US-Herceptin and EU-Herceptin compared to MYL-1401O. Asn 30 is located in the CDR and is likely the most critical deamidation site with respect to efficacy. However, the analytical similarity assessment binding data and data from other potency assays indicate that the differences seen here do not significantly impact in vitro potency.*

Functional activity

ADCC activity was determined for each fractionated charge group. The highly acidic peak groups clearly show lower ADCC activity than the main and basic variants of all three products. The conclusions regarding other peak groups are not clear (see Table 3.2.3.2/33 below).

Reviewer comment: *Because the data for the US-Herceptin material is significantly different than the data for the MYL-1401O material, and the differences in the contents of the peak groups across products are not sufficiently large to account for the differences in activity, the impact to potency associated with the different peak groups cannot be assigned. However, this appears to be an issue associated with fractionation and the ADCC assay and does not necessarily impact the determination of analytical similarity.*

Table 3.2.S.3.2/ 33: Relative ADCC Activity for MYL-1401O and Herceptin Variants

Variant ID	Batches/Product		
	MYL-1401O	EU Herceptin	US Herceptin
A4+A5 variant	0.53	0.60	0.59
A3 variant	0.75	0.78	0.68
A2 variant	0.76	0.83	0.38
A2* variant	0.77	NAP	NAP
A1 variant	0.57	0.75	0.29

Main variant	0.78	0.93	0.83
B1 variant	0.76	0.87	1.21
B2 variant	0.80	1.08	1.14
B3 variant	0.81	0.93	0.94

NAP: as variant is not present in Herceptin

Reviewer comment: *The analytical similarity data for charge heterogeneity show lower levels of acidic variants in the MYL-1401O lots compared to the US-Herceptin and EU-Herceptin lots. The difference appears to be due in large part to different levels of deamidation, predominantly at Asn 30. From an analytical similarity perspective, the overall ADCC, HER2 binding, and inhibition of proliferation data indicate that the difference in this variant, or other charge-related variants, is not sufficient to significantly impact potency; the FcRn binding data indicate that the differences are not likely to significantly impact PK.*

While multiple sites of Asn modifications were assessed in the characterization study, the isomerization of Asp 102 (isoAsp 102) in the heavy chain of the CDR was not evaluated (no data provided in original submission or IR response). IsoAsp 102 has been reported in the literature to significantly reduce the potency of trastuzumab. Typically, isoAsp modifications of monoclonal antibodies result in an increase in basic species. While no difference was shown in overall basic species among the three products in the analytical similarity assessment, the comparative stability study (see discussion below in Comparative Stability section) shows an increase in basic species among all three products after three months storage under stressed conditions, and MYL-1401O lots significantly more basic species than US-Herceptin and EU-Herceptin. This increase in basic species content also correlated with a decrease in HER2 binding. The increase in basic species and decrease in potency may be related to isoAsp 102 content. The formation of basic species of MYL-1401O was considered as part of the overall control strategy for MYL-1401O.

The charge variant analysis supports a demonstration of analytical similarity between MYL-1401O and US-Herceptin and establishment of the analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.7.2 Charge variants by capillary isoelectric focusing (cIEF) – Tier 3

An additional assessment of charge variants based on isoelectric point (pI) was conducted using cIEF. Overlays of electropherograms show consistency of pI profiles; however, there is some variability in the peak areas among the three products. The ranges of acidic, basic and main peak content for 16 lots of US-licensed Herceptin, 26 lots of EU-Herceptin, and 12 lots of MYL-1401O DP are:

- US-Herceptin lots: basic – 3.2-7.2%, main – 57.8-66.7%, acidic – 28.6-39.0%,
- EU-Herceptin lots: basic – 3.1-5.7%, main – 61.0-68.0%, acidic – 28.1-35.2%,
- MYL-1401O lots: basic – 2.2-3.8%, main – 62.1-70.0%, acidic – 27.3-35.3%

The pIs of the basic and main peaks were 8.8 and 8.7, respectively, for all three drug products, and the pI ranges of the acidic peaks were 8.0-8.5 for US-Herceptin, 8.0-8.5 for EU-Herceptin, and 8.2-8.5 for MYL-1401O. As for the IEX-HPLC data, the scatter plots of the cIEF charge species show slightly lower levels of acidic species compared to US-Herceptin and EU-

Herceptin lots. However, in the cIEF analysis, it appears that the MYL-1401O DP lots have a lower level of basic variants (mean 2.8%) than the US-Herceptin (mean 4.9%) and EU-Herceptin (mean 4.1%) lots, which was not observed in the IEX-HPLC analysis.

Reviewer comment: *The slightly lower levels of cIEF basic species in MYL-1401O lots compared to US-Herceptin and EU-Herceptin may be at least partially attributed to the slightly lower amount of C-terminal lysine detected in MYL-1401O lots (0.1-0.6%) compared to US-Herceptin (0.7%) and EU-Herceptin (1.1%). There are lower overall levels of basic variants observed using cIEF than IEX-HPLC, and this may indicate that the basic peak species separated using cIEF may be predominantly the C-terminal lysine variants, which are quite basic; the stability data discussed below also support that the cIEF basic variants are composed of predominantly C-terminal lysine. A difference in these variants is not expected to have a clinical impact. Overall, the cIEF analysis supports similarity between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridge.*

6.1.7.3 Hydrophobic Interaction Chromatography (HIC) – Tier 3

HIC provides an orthogonal approach for the evaluation of modifications such as oxidation. Ten lots of US-Herceptin, nine lots of EU-Herceptin and eight lots of MYL-1401O were evaluated. The HIC chromatogram profiles were similar for all three products, with no peaks detected in MYL-1401O that were not also present in US-Herceptin or EU-Herceptin, suggesting the presence of the same types of modifications. The average content of less hydrophobic species (LHS), main peak and more hydrophobic species (MHS) are:

- US-Herceptin: LHS – 12.41%; main – 73.07%; total MHS – 14.52%
- EU-Herceptin: LHS – 11.93%; main – 73.95%; total MHS – 14.12%
- MYL-1401O: LHS – 10.21%; main – 76.97%; total MHS – 12.82%

Reviewer comment: *Lower levels of LHS and MHS were detected in MYL-1401O lots compared to US-Herceptin and EU-Herceptin lots. This difference correlates with the variability observed in the degradation-related modification species (see discussion in Section 6.1.7.1). The data support similarity between the MYL-1401O and US-Herceptin lots, and the establishment of the analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.7.4 Glycated IgG using Boronate Affinity Chromatography – Tier 3

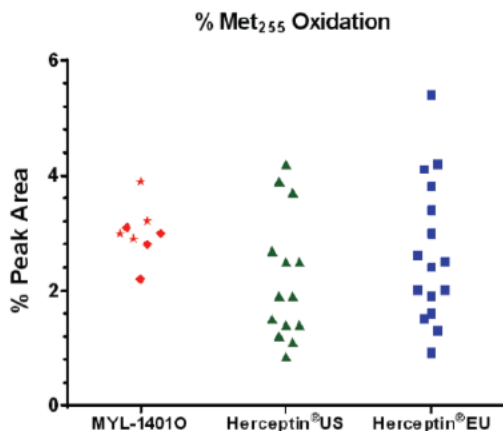
Boronate affinity chromatography was used to evaluate glycation in 15 lots of US-Herceptin, 17 lots of EU-Herceptin and 11 lots of MYL-1401O. The percent glycation ranges were: US-Herceptin – 3.3-6.0%, EU-Herceptin – 3.3-5.9%, and MYL-1401O – 3.3-4.9%.

Reviewer comment: *The glycation content was similar in MYL-1401O, US-Herceptin and EU-Herceptin lots. The data support a demonstration of highly similar and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.7.5 Oxidation by reduced peptide mass fingerprinting – Tier 3

The oxidation of M255 located in the Fc region of the HC was analyzed by peptide mass fingerprinting of 14 lots of US-Herceptin, 16 lots of EU-Herceptin, and 8 lots of MYL-1401O. The M255 oxidation content ranges for the three products are: US-Herceptin – 0.85-4.2%, EU-Herceptin – 0.92-5.4%, and MYL-1401O DP – 2.2-3.9%. The data show that M255 content is more variable in the US-Herceptin and EU-Herceptin lots compared to the MYL-1401O lots. The levels of oxidized M255 in the MYL-1401O DP lots were within the ranges of M255 oxidation determined for US-Herceptin and EU-Herceptin lots (Figure 59, below).

Figure 50: Scatter Plot Distribution of Oxidized Met255 Species in MYL-1401O, EU-Approved Herceptin and US-Licensed Herceptin Lots



Reviewer comment: This peptide mapping analysis was consistent with the peptide mapping data provided in the June 2, 2017 response to IR that showed similar levels of M255 oxidation in MYL-1401O, US-Herceptin, and EU-Herceptin. The M255 oxidation data support a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of analytical bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.7.6 Subvisible particles (SVP) - Tier 3

An assessment of SVP was conducted using micro-flow imaging (MFI). Data (per container) from six lots of US-Herceptin, six lots of EU-Herceptin, and 12 lots of MYL-1401O DP were:

- US-Herceptin – 2 µm: 1457-5211, 5 µm: 185-690, 10 µm: 25-83, 25 µm: 2-6
- EU-Herceptin - 2 µm: 719-6574, 5 µm: 92-677, 10 µm: 10-156, 25 µm: 0-16
- MYL-1401O 420 mg - 2 µm: 5937-20512, 5 µm: 240-1331, 10 µm: 18-189, 25 µm: 1-21
- MYL-1401O 150 mg– 2 µm: 930-22979, 5 µm: 78-857, 10 µm: 8-161, 25 µm: 1-16

The range of the number of SVPs ≥ 10 µm and ≥ 25 µm were within the compendial limits of ≤ 6000 and ≤ 600 particles per container, respectively.

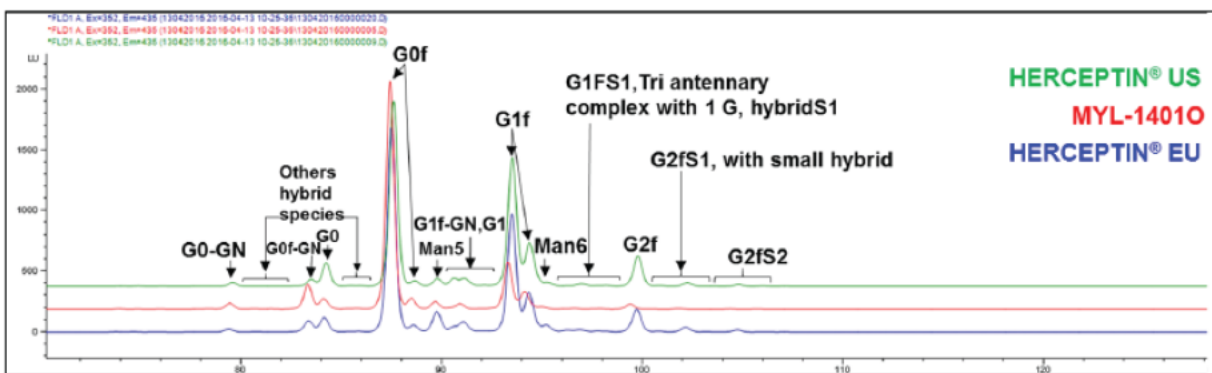
Reviewer comment: Generally, the MYL-1401O DP lots had higher amounts of SVPs of all sizes compared to the US-Herceptin and EU-Herceptin lots, and there is only moderate correlation with the presentation-based container volumes. The magnitude of the difference is minor for the 10 µm and 25 µm particles. Both formulation and processing may impact the formation of SVPs. MYL-1401O includes PEG3350 as a (b)(4) in the formulation, while US-Herceptin and EU-

Herceptin contain polysorbate 20. High levels of SVPs have been related to the induction of immunogenicity and the potential to impact PK and efficacy. However, the clinical studies indicate no significant difference in safety, efficacy, PK or immunogenicity among MYL-1401O, US-Herceptin and EU-Herceptin and suggest that the differences in SVPs observed are likely not clinically meaningful.

6.1.8 Glycosylation Assessment – Tier 2

The glycosylation profiles of 19 US-Herceptin, 22 EU-Herceptin, and 11 MYL-1401O DP lots were resolved by NP-HPLC coupled with fluorescent detection. A representative chromatogram (Figure 51, below) of the glycosylation profiles for the three products shows the 13 peak groups identified [G0-GN; G0f-GN; G0; G0f; Mannose 5 (man5); G1f-GN, G1; G1f; Mannose 6 (man6); G1fS1, tri-antennary complex with 1G, hybrid S1; G2fS1, with small hybrid; and G2fS2, other hybrid species].

Figure 51: Representative Overlaid N-Glycan Profiles of MYL-1401O, EU-Approved Herceptin and US-Licensed Herceptin

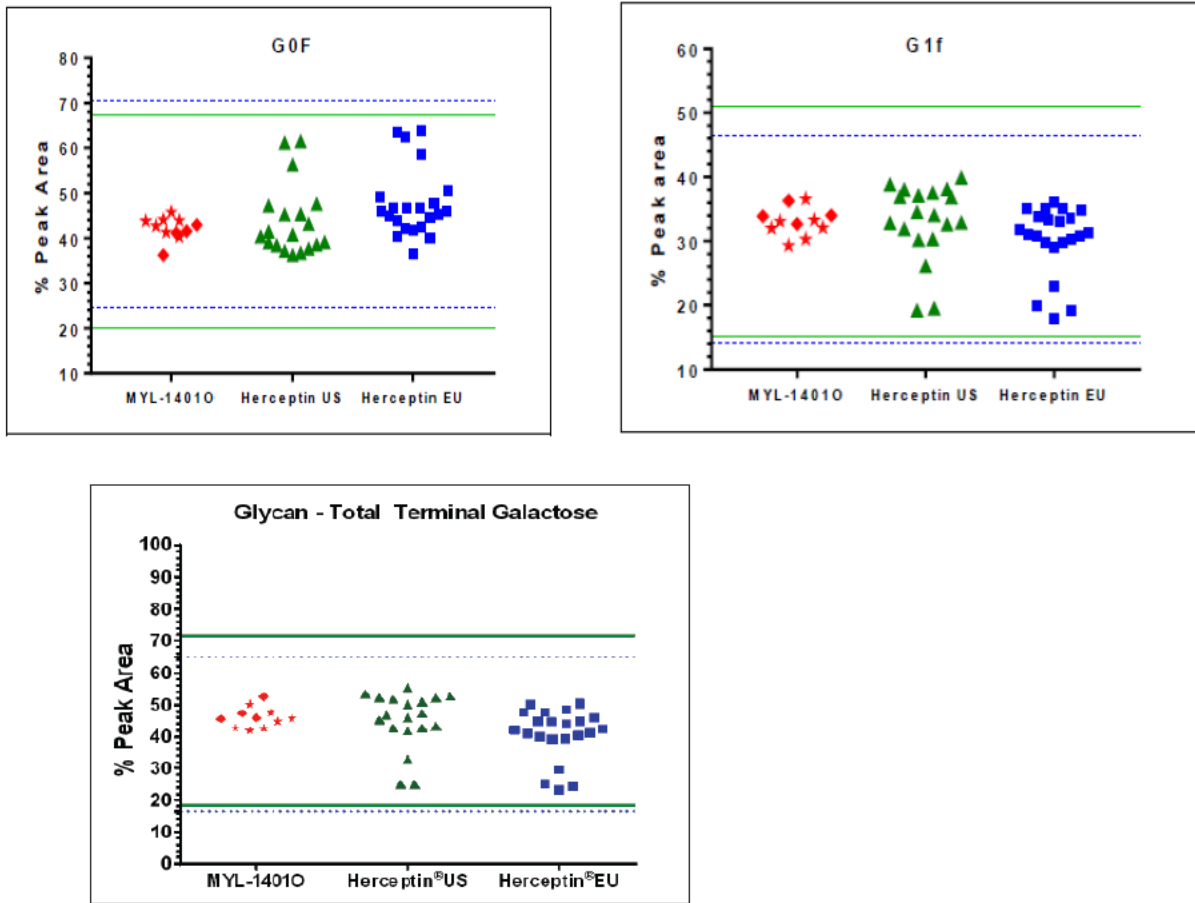


In response to an IR dated March 27, 2017, a quantitative analysis of the content of each glycoform present in the MYL-1401O, US-Herceptin and EU-Herceptin lots was provided in the Comparability and Analytical Assessment Annexure 1 (Section 3.2.R). Scatter plots of the data are presented below (Figure 1).

G0f and G1f comprise the majority of the glycoforms observed. The G0f and G1f content present in MYL-1401O lots is within the G0f and G1f QR of the US-Herceptin and EU-Herceptin lots. The levels of G0f-GN; G2f; G1f-GN, G1; G2fS2; G1fS1 tri-antennary complex; and other hybrid glycosylated species present in MYL-1401O lots are also within the range of the US-Herceptin and EU-Herceptin lots.

The total terminal galactose levels were also evaluated as a Tier 2 attribute. Total galactose levels for 19 lots of US-Herceptin, 22 lots of EU-Herceptin, and 11 lots of MYL-1401O are shown in Figure 53, below. The MYL-1401O levels were within the QR of both US- and EU-Herceptin.

Figure 1: Scatter Plot Distribution of 13 Glycan Species in MYL-14010, US-Licensed Herceptin and EU-Approved Herceptin Lots



Solid Green lines represents the Quality Range (Mean±3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean±3SD) established for EU-approved Herceptin

Among the afucosylated glycoforms, the ranges of G0, G0-GN, and man5 in the MYL-14010 lots are within the QR of the US-Herceptin and EU-Herceptin lots. Two or three MYL-14010 lots have slightly higher levels of man 6/(G1f-GN) S1 content compared to the US-Herceptin and EU-Herceptin ranges, respectively.

Figure 53 (below) shows the Tier 2 analysis of the combined peak area for man5 and man6. The high mannose levels in MYL-14010 are within the QR of the US-Herceptin lots but clear differences are observed. The high mannose levels in MYL-14010 are not within the EU-Herceptin QR.

The level of total afucosylated species was evaluated using these NP-HPLC data and using a method to specifically assess afucosylation (see below). Total afucosylated species levels are shown in the final figure below. The levels of afucosylation in MYL-14010 lots were within the ranges in the US- and EU-Herceptin lots.

Reviewer comment: Afucosylated glycans play a role in Fc-receptor binding and ADCC activity. Total afucosylated species is discussed below.

Antibodies with high levels of high mannose (e.g., man5 and man6) content have been associated with increased antibody clearance and decreased efficacy. The man5 content is higher in a portion of MYL-14010 lots compared to US-Herceptin and EU-Herceptin, although MYL-14010 lots are within the US-Herceptin QR, and the levels of man6, in combination with a co-eluting glycoform, are higher in a number of MYL-14010 lots. The differences in high mannose content did not result in a difference in PK among the three products as shown in the associated clinical study reports.

Given the magnitude of the differences observed, clinical impact is not expected, and the clinical data support this conclusion. The differences do not preclude a conclusion of high similarity between US-Herceptin and MYL-14010 and support the establishment of the analytical bridge among products.

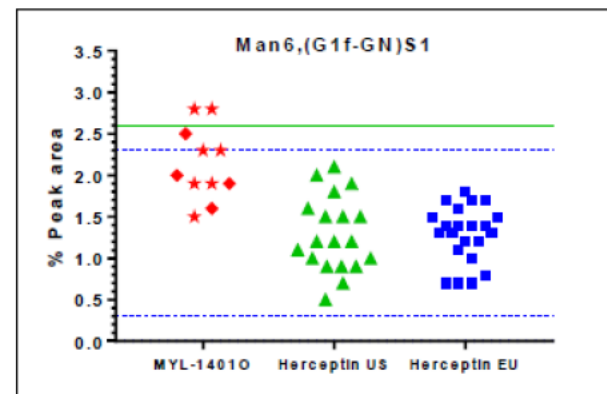
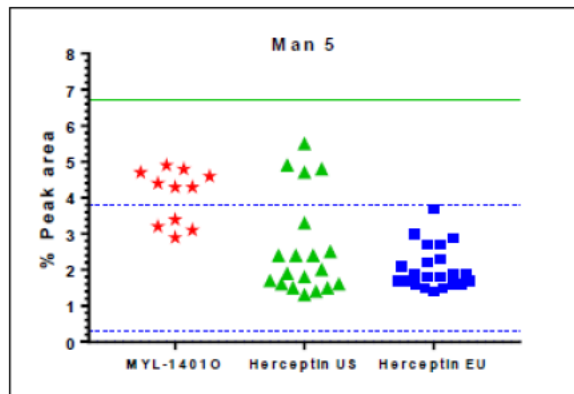
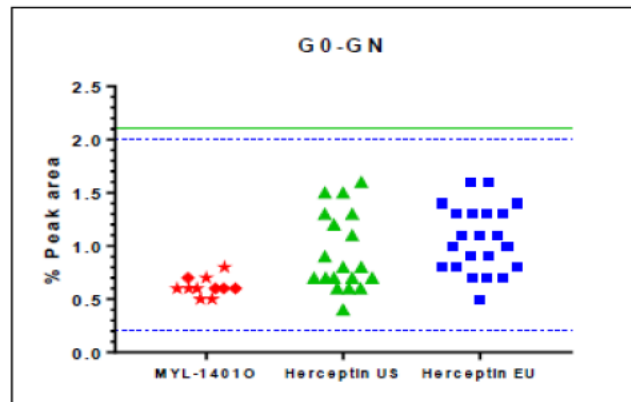
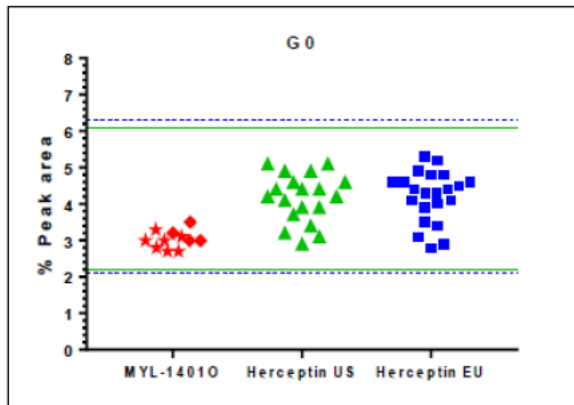
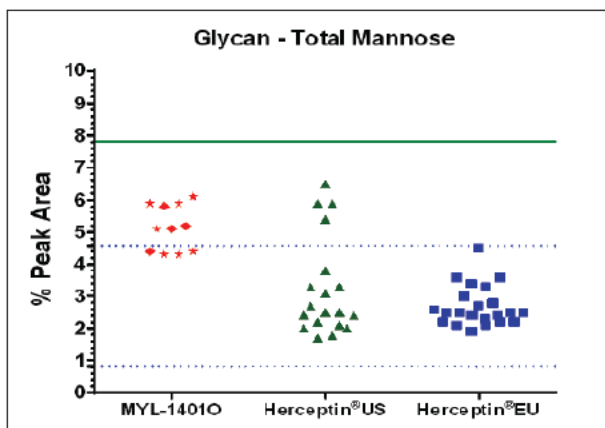
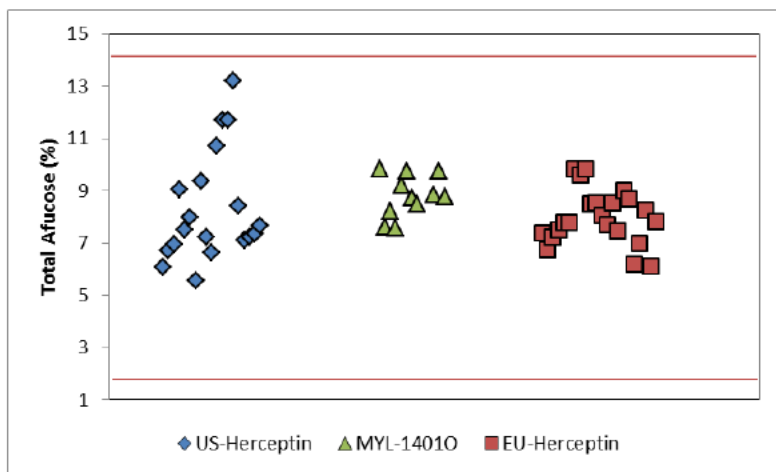


Figure 53: Scatter Plot Distribution of Total High Mannose and Total Terminal Galactose Content in MYL-1401O, US-Licensed Herceptin, and EU-Approved Herceptin Lots



Solid Green lines represents the Quality Range (Mean±3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean±3SD) established for EU-approved Herceptin

Total Fucose

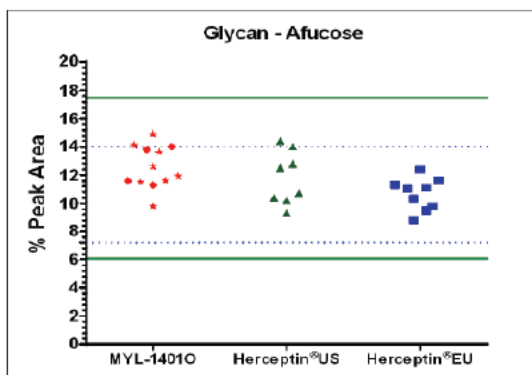


Graph generated by CMC reviewer

6.1.8.2 Total afucosylation analysis by RP-HPLC-MS –Tier 2

Afucosylation was assessed by RP-HPLC-MS. Data from the assessment of 8 lots of US-Herceptin, 9 lots of EU-Herceptin, and 12 lots of MYL-1401O DP show similar levels of afucosylated species (Figure 54, below). The ranges of afucosylation for the three products were: US-Herceptin – 9.3-14.4%, EU-Herceptin – 8.8-12.4%, and MYL-1401O DP – 9.8-14.9%. The MYL-1401O lots and EU-Herceptin lots are within the US-Herceptin QR. However, two lots of MYL-1401O and one lot of US-Herceptin was outside the EU-Herceptin QR.

Figure S4: Scatter Plot Distribution of Afucosylated Variants for MYL-1401O, US-Licensed Herceptin and EU-Approved Herceptin Lots



Solid Green lines represents the Quality Range (Mean±3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean±3SD) established for EU-approved Herceptin

Reviewer comment: Both methods used show similar levels of afucosylated species between US-Herceptin and MYL-1401O, although there may be a slightly higher trend in MYL-1401O. The levels of afucosylation in some lots of MYL-1401O and US-Herceptin were higher than those in EU-Herceptin. However, both the ADCC data and the FcγRIIIa binding data demonstrate statistical equivalence or similarity, respectively, among the three products. Therefore, the minor difference in afucosylation is not likely to have clinical impact and do not preclude a determination of highly similar between US-Herceptin and MYL-1401O or the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

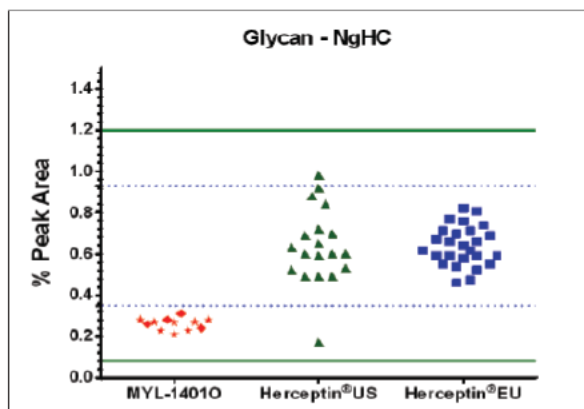
6.1.8.3 Non-glycosylated heavy chain (NG-HC) analysis by CE-SDS reduced –Tier 2

Antibody aglycosylation has been correlated with loss of effector function, increased aggregation and conformational changes in the molecule. To evaluate NG-HC content, 19 lots of US-Herceptin, 26 lots of EU-Herceptin, and 12 lots of MYL-1401O were assessed by CE-SDS under reduced conditions. Representative electropherogram overlays show consistent profiles. Quantitative results for NG-HC, LC, HC and p75 content are shown in the scatter plot below (Figure 56). The ranges for each fragment are:

- US-Herceptin – NG-HC: 0.17-0.98%, p75: 0.16-0.31; HC: 66.4-68.0%, LC: 31.2-32.5%
- EU-Herceptin – NG-HC: 0.46-0.82%, p75: 0.10-0.27; HC: 66.3-68.1%, LC: 31.1-33.1%
- MYL-1401O – NG-HC: 0.21-0.31%, p75: 0.26-0.40; HC: 67.7-68.2%, LC: 31.3-33.0%

p75 is generated by a non-reducible thioether bridge between the LC and HC of the molecule. The p75 content of MYL-1401O lots is slightly higher than the US-Herceptin and EU-Herceptin lots. The potential impact on biological activity resulting from an increase in p75 is unclear; however, the levels are less than 0.5%.

Figure 56: Scatter Plot Distribution of Non-Glycosylated Heavy Chain (Ng-HC) Content in MYL-1401O, US-Licensed Herceptin and EU-Approved Herceptin Lots



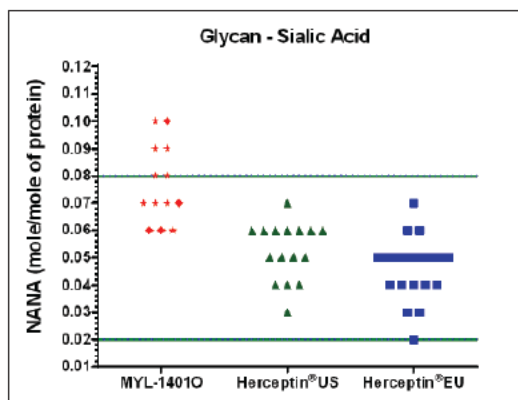
Solid Green lines represents the Quality Range (Mean $\pm$ 3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean $\pm$ 3SD) established for EU-approved Herceptin

Reviewer comment: One lot of US-Herceptin had much lower NG-HC content (0.17%) than the other 18 US lots, resulting in expansion of the range of NGHC content, so that the MYL-1401O lots are within the US lot range. However, the overall data show that MYL-1401O lots have significantly lower NG-HC content compared to both the US-Herceptin and EU-Herceptin lots. Low NG-HC content has the potential to impact product efficacy through ADCC activity. However, the overall content of NG-HC is low among all three products, and equivalence in ADCC activity among MYL-1401O, US-Herceptin and EU-Herceptin has been demonstrated (see Section 6.1.3.3). In addition, no differences were identified in the clinical studies evaluating MYL-1401O. Therefore, the difference in NG-HC has been shown to not have clinical impact and does not preclude a determination of high similarity between MYL-1401O and US-Herceptin or the establishment of the analytical portion of the scientific bridges among products.

6.1.8.4 Total sialic acid content by RP-HPLC – Tier 2

Terminal sialic acid content has been correlated with a decrease in FcRn binding and increased antibody clearance. Total terminal sialic acid content (N-acetyl Neuraminic acid, NANA) was determined by RP-HPLC analysis for 16 lots of US-Herceptin, 24 lots of EU-Herceptin, and 13 lots of MYL-1401O DP. The ranges are: US-Herceptin – 0.03-0.07%, EU-Herceptin – 0.02-0.07%, MYL-1401O DP – 0.06-0.10%. The results of the sialic acid analysis, plotted in Figure 57 (below), show a slight increase in sialic acid present in MYL-1401O lots compared to US-Herceptin and EU-Herceptin. Four of the 13 MYL-1401O lots were outside both the US- and EU-Herceptin QR. However, the overall percent of sialic acid present is very low (no more than 0.10%). No NGNA was detected in MYL-1401O.

Figure 57: Scatter Plot Distribution of Sialic Acid Content in MYL-1401O, US-Licensed Herceptin and EU-Approved Herceptin Lots



Solid Green lines represents the Quality Range (Mean $\pm$ 3SD) established for US-licensed Herceptin
Dotted Blue lines represents the Quality Range (Mean $\pm$ 3SD) established for EU-approved Herceptin

Reviewer comment: NANA content is detected at very low levels among the three products. Levels this low are not likely to have clinical impact, which is supported by the clinical studies evaluating PK among the three products. Therefore, the difference in sialic acid levels does not preclude a determination of high similarity between US-Herceptin and MYL-1401O or the establishment of the analytical portion of the scientific bridges among products.

Assessment of primary, secondary and higher order structure

6.1.9.1 Primary sequence analysis by reduced peptide mapping using RP-HPLC –Tier 3

Primary sequence analysis was conducted by RP-HPLC-UV peptide mapping under non-reducing and reducing conditions. The chromatogram profiles were similar among MYL-1401O, US-Herceptin, and EU-Herceptin. The same peptide fragments were identified among the three products, and mass analysis of the HC and LC fragments generated under reduced and non-reduced conditions showed identical masses.

Reviewer comment: The primary sequences of the three products are identical.

6.1.9.2 Intact mass by LC-ESI-MS – Tier 3

Intact molecular mass analysis of 16 lots of US-Herceptin, 23 lots of EU-Herceptin, and 12 lots of MYL-1401O was conducted using LC-ESI-MS. Representative electropherograms provided for each product show six glycosylated peaks with consistent peak areas in each product. The ranges of the intact masses are: US-Herceptin – 148049-148067 Da, EU-Herceptin – 148050-148068 Da, and MYL-1401O – 148051-148062 Da.

Reviewer comment: The data show similar masses for MYL-1401O, US-Herceptin, and EU-Herceptin, which correlate to the expected mass of trastuzumab. The intact mass analysis supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

6.1.9.3 Reduced mass by LC-ESI-MS –Tier 3

The masses of the LCs and HCs of 14 lots of US-Herceptin, 20 lots of EU-Herceptin, and 10 lots of MYL-1401O DP were evaluated by LC-ESI-MS following reduction by DTT. The LC and HC mass data are:

- US-Herceptin – LC: 23728-23728 Da; HC: 51226-51234 Da
- EU-Herceptin – LC: 23727-23729 Da; HC: 51228-51233 Da
- MYL-1401O – LC: 23727-23728 Da; HC: 51230-51232 Da.

***Reviewer comment:** The data support a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.9.4 Disulfide linkage by RP-HPLC – Tier 3

Trastuzumab has 16 disulfide bonds, including 12 intra-chain and 4 inter-chain linkages. The disulfide linkages of MYL-1401O, US-Herceptin and EU-Herceptin were assessed by RP-HPLC. Chromatogram overlays of replicates of the three products show similar profiles containing seven disulfide linked peptide associated peaks (and a reference peak, H[374-395]). The HC-LC disulfide bond was not identified for any of the three products. The observed masses of the disulfide linked peptide peaks were identical among MYL-1401O, US-Herceptin and EU-Herceptin and were similar to the theoretical masses.

***Reviewer comment:** The lack of identification of one of the expected disulfide bonds is discussed in the characterization section. The disulfide bond analysis supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.9.5 Free cysteine analysis –Tier 3

The free cysteine content was determined for 17 lots of US-Herceptin, 15 lots of EU-Herceptin, and seven lots of MYL-1401O DP using Ellman's reagent. The reported levels of free cysteine residues for all three products were below the limit of quantitation (BQL = 3 µM of free cysteine).

***Reviewer comment:** The data suggest that there are no free cysteines present and that the expected disulfide bonds present in the three products are fully formed.*

6.1.9.6 Secondary structure by Far UV circular dichroism (CD) – Tier 2

Secondary structure was assessed by far UV CD in the spectral region of 190-250 nm, and data were reported for 17 lots of US-Herceptin, 21 lots of EU-Herceptin, and 11 lots of MYL-1401O DP. Representative overlays show similar spectral profiles among the three products. The ranges of percent beta-sheets and beta-turns are: US-Herceptin – beta-sheets: 72.8-90.2%, beta-

turns: 9.8-27.2%; EU-Herceptin – beta-sheets: 68.2-89.8%, beta-turns: 10.2-31.8%; and MYL-1401O – beta-sheets: 75.3-87.4%, beta-turns: 12.6-24.7%.

Reviewer comment: *The far UV spectral analysis shows similarity among the secondary structures of MYL-1401O, US-Herceptin lots and EU-Herceptin. Minor variability in the quantitative data for percent beta sheets and beta turns was shown; however, variability is expected for the far UV CD analytical method.*

6.1.9.7 Secondary structure by fourier transform infrared spectroscopy (FTIR) – Tier 3

Secondary structure was also assessed using FTIR. Data from four lots of US-Herceptin, five lots of EU-Herceptin and seven lots of MYL-1401O show similar content of alpha-helix, beta-sheet, beta-turn, other (undefined peak), amide I, and amide II. An overlay of representative profiles for US-Herceptin, EU-Herceptin and MYL-1401O also showed consistent spectra.

Reviewer comment: *The overall assessment of secondary structure supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridges among US-Herceptin, EU-Herceptin, and MYL-1401O.*

6.1.9.8 Tertiary structure by Near UV-CD – Tier 3

Tertiary structure was assessed by near UV-CD analysis of the aromatic amino acid side chains detected in the spectral region of 320-260 nm. Spectral overlays from the assessment of 17 US-Herceptin lots, 21 EU-Herceptin lots and 11 MYL-1401O lots show similar profiles, suggesting consistent tertiary structure among the three products.

Reviewer comment: *The near UV spectral analysis supports a demonstration of highly similar between MYL-1401O and US-Herceptin and the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.*

6.1.9.9 Higher order structure by differential scanning calorimetry (DSC) – Tier 3

DSC was used to determine the thermodynamic differences for four lots of US-Herceptin, three lots of EU-Herceptin and three lots of MYL-1401O DP. A representative overlay of the resulting thermograms show similar profiles among the three products. Consistent with the thermogram overlay, the quantitative data show similarity among the Tm1 and Tm2 values.

Reviewer comment: *The DSC analysis demonstrates structural similarity among the three products.*

6.1.9.10 Higher order structure by intrinsic fluorescence – Tier 3

Intrinsic fluorescence analysis was used as an orthogonal method to assess tertiary structure. The assessment was conducted on four lots of US-Herceptin, five lots of EU-Herceptin and eight lots of MYL-1401O DP. The λ_{max} (nm) values showed similar ranges among the three products as follows. Spectral overlays also show similarity among the three products.

Comparative Stability

To support a demonstration of highly similar, the degradation profiles of MYL-1401O DP (150 mg and 420 mg), US-Herceptin, and EU-Herceptin lots were investigated in comparative forced degradation and in-use stability studies. For the forced degradation studies, MYL-1401O, US-Herceptin, and EU-Herceptin were investigated in both the lyophilized state and after reconstitution. The conditions included temperature stress (accelerated and stressed), light exposure, oxidative stress and hydrolysis (acid/base), and select physical, chemical and functional quality attributes were assessed.

1. Forced Degradation

Two MYL-1401O (one 150 mg and one 420 mg) DP lots, one US-Herceptin lot, and one EU-Herceptin lot were evaluated in the forced degradation studies. The age at the time of analysis ranged from 4 to 42 months for the MYL-1401O lots, 10 to 31 months (assumed) for the US-Herceptin lots, and 13 months (assumed) for the EU-Herceptin lots.

Lyophilized State

Lyophilized product was exposed to 25°C/60% RH or 40°C/75% RH conditions for 0.5, 1, 2, 3, and 6 (25°C only) months or was exposed to 1.2 or 2.4 M lux hours and was then subjected to pH, SEC, protein concentration, IEX, CE-SDS, CD, fluorescence, cIEF, and biological assay analyses.

Temperature Stress:

- Following three months of storage at 40°C ± 2°C/ 75% RH ± 5% RH (Tables 3.2.P.8.3/17-19):
 - No significant differences were observed in appearance (before and after reconstitution), protein concentration or higher order structure.
 - Size variants: An increase in SEC HMWS was observed for MYL-1401O 150 mg (~ 2.6%), MYL-1401O 420 mg (2.60%), US-Herceptin (~2.8%), and EU-Herceptin (~2.8%). The increase in HMWS correlated with a minor decrease in monomer content. No changes were noted in LMWS content in all four presentations.

By CE-SDS non-reduced, relatively consistent increases were observed in LC, HC/Fab, 2H, and 2H1L fragments over time for all four products, resulting in similar increases in total fragment of 1.2% for US-Herceptin, 1.5% for MYL-1401O 420 mg, 1.4% for EU-Herceptin, and 0.8% for MYL-1401O 150 mg. By CE-SDS reduced, no significant changes were observed in LC, HC, or NG-HC for all four products. However, increases in the p75 thioether impurity was noted for all four molecules: ~0.5% for US-Herceptin, ~0.4% for MYL-1401O 420 mg, ~0.3% for EU-Herceptin, and ~0.3% for MYL-1401O 150 mg.

- Charge variants: By IEX, an increase in basic species was observed for MYL-1401O 420 mg (12.9%), MYL-1401O 150 mg (14%), US-Herceptin (5.3%), and EU-Herceptin (4.4%). No changes were noted in acidic species in all four presentations. The same trends in basic, main and acidic variants were observed in the cIEF assessment.

Reviewer comment: *No information was provided regarding the species that changed. As previously discussed, according to literature, isoAsp 102 has been shown to decrease the potency of trastuzumab (see discussion in Section 6.1.7.1). Reflective of the reports in the literature regarding isoAsp 102 and basic charged species detected in trastuzumab, the increase in basic species observed correlates with a decrease in binding for all lots. Mylan did not provide an evaluation of isoAsp 102 in the characterization study. Given that this study was performed under a more extreme stress condition than the 25°C study (below), while it is not clear that there is a significant difference between MYL-1401O and US- and EU-Herceptin, basic species concerns have been considered as part of the evaluation of the basic species-related aspects of the control strategy for MYL-1401O.*

- No trending was observed in M255 oxidation, with the exception of a slight increase in the EU-Herceptin lot (~1.4%).
- Functional assessment: A decreasing trend was observed for HER2 binding affinity (cell based BT-474 assay) for US-Herceptin (from 1.02 to 0.79), MYL-1401O 420 mg (from 1.11 to 0.76), EU-Herceptin (from 1.07 to 0.81) and MYL-1401O 150 mg (from 0.91 to 0.78). However, this apparent decrease in HER2 binding did not correlate with any trending in ADCC activity or inhibition of proliferation. Also, no trending was observed in FcγRIIIa binding affinity.
- Following six months of storage at 25°C ± 2°C/ 60% RH ± 5% RH (Tables 3.2.P.8.3/20-22): Results and trending were similar to those observed following storage under 40°C conditions, but the increases in HMWS by SEC-HPLC were not as high and no trending was observed in HER2 binding. The increase in basic species was apparent; however, the differences between MYL-1401O and US- and EU-Herceptin were not (increases of 2.4%/2.6% and 3.9%/2.9%, respectively)

Photo Stress:

- Following maximum exposure of 2.4 M lux hours (Tables 3.2.P.8.3/23-25):
 - No significant differences were observed in appearance (before and after reconstitution), protein concentration or higher order structure.
 - Size variants: By SEC-HPLC, an increase in HMWS was observed for MYL-1401O 150 mg (0.46%), MYL-1401O 420 mg (0.58%), US-Herceptin (0.44%), and EU-Herceptin (0.43). No changes were noted in LMWS content in all four presentations.

By CE-SDS non-reduced, increases were observed in LC, HL, 2H, and 2H1L fragments for all four presentations. However, an increase in HC/Fab was only shown for MYL-1401O 420 mg (from 0.06 to 0.46%) and 150 mg (from 0.13 to 0.34%). An increase in total impurities was observed for US-Herceptin (~15%), for MYL-1401O 420 mg (~4%), for EU-Herceptin (~9%), and for MYL-1401O 150 mg (~6%). The degradation for all products is driven mainly by formation of 2H1L. By CE-SDS reduced, decreases were observed in HC+LC for US-Herceptin (2.7%), MYL-1401O 420 mg (5.4%), EU-Herceptin (2.3%), and MYL-1401O 150 mg (5.0).

- Charge variants: By IEX, an increase in acidic and basic species was observed for all four molecules. By cIEF, an increase in acidic variants, but not basic variants, was observed for all three products.
- No trending was observed in M255 oxidation, with the exception of a slight increase noted in the MYL-1401O 420 mg lot (0.68%).
- Functional assessment: No trending was observed in FcγRIIIa binding or in potency by inhibition of proliferation, HER2 binding and ADCC activity for all four products.

Liquid (Reconstituted) State

Table 3.2.P.8.1/8 (below) summarizes the comparative forced degradation protocol employed for the assessment of each product following reconstitution in the appropriate volume of WFI to result in a 21 mg/ml solution.

Table 3.2.P.8.1/ 8: Protocol for Comparative Forced Degradation Study – Liquid State of DP

Stress Factor / Parameter	Temperature										Chemical Treatment				pH						Photo Treatment											
	2 - 8°C (control)		25°C				40°C				Peroxide (0.1% TBHP)				pH 3 at 25°C						pH 9 at 25°C						Dark control		Photo exposure			
Condition	0	1	4	10	4	6	8	10	0*	1	2	4	8	0*	2	4	6	8	10	0*	2	4	6	8	10	1.2	0.3	0.6	0.9	1.2		
	Time Points	Days																				M lux hours										
SEC / Visual inspection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
IEX	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Protein concentration (UV)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
CE-SDS nonreducing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
CD and intrinsic tryptophan fluorescence	✓	✓	0 and T _{end} ⁺																													
Biological assays ¹	(0 and T _{end} ⁺) ²																															
Oxidation (peptide mapping)	✓	✓	(0 and T _{end} ⁺) ²										✓	✓	✓	✓	✓	(0 and T _{end} ⁺) ²										✓	✓	✓	✓	✓

✓-Tests to be performed; 0* - Time point just after the addition of the stress agent (acid/base/TBHP). Sample would be analysed/frozen immediately for future analysis; T_{end}⁺ - Last (End) time point; ¹ - Biological assays includes HER2 Binding assay by flow cytometry using SK-BR-3 cells and FcγRIIIa receptor binding assay; ² - Biological assay and oxidation peptide mapping experiments, wherever applicable will be performed at T0 and T_{end}⁺, if T_{end}⁺ fails the acceptance criteria for bioassay or beyond the method variability for peptide mapping, then experiments will be done for time points preceding T_{end}⁺, until results pass the acceptance criteria or lie within the method variability range from T0.

Temperature Stress:

- Following 10 days storage at 2-8°C/control (Table 3.2.P.8.3/26): No significant trending was observed in size variants by SEC-HPLC, charge variants by IEX-HPLC, higher order structure by IF, fragments by CE-SDS non-reduced, secondary structure by far-UV-CD, HER2 binding or FcγRIIIa binding.
- Following 10 days storage at 40°C (Tables 3.2.P.8.3/27):
 - No significant differences were observed in protein concentration, higher order structure by IF, or secondary structure by far UV-CD for all four products.
 - Size variants: By SEC-HPLC, no trending was observed in HMWS or monomer content for all four product lots.

By CE-SDS non-reduced, minor increases in fragments were observed for all products. The decrease in monomer was ≤1.0% for all materials.

- Charge variants: By IEX, there are major changes in charge species for all four products. For MYL-1401O 150 mg, acidic variants increased by ~11% and basic variants increased by ~11%. For MYL-1401O 420 mg, acidic variants increased by ~8% and basic variants increased by ~11%. For US-Herceptin, acidic variants increased by ~18% and basic variants increased by ~9%. For EU-Herceptin, acidic variants increased by ~10% and basic variants increased by ~9%.

- Functional assessment: No trending was observed in HER2 relative binding or FcγRIIIa binding for all four products.
- Following ten days of storage at 25°C (Table 3.2.P.8.3/28): No significant changes or trends were observed for all quality attributes assessed, with the exception of charge variants by IEX-HPLC. There were ~2% increases in basic variant for MYL-1401O 420 mg, US-Herceptin, and EU-Herceptin and a ~3% increase for MYL-1401O 150 mg. There was also a ~9% increase in acidic variant for US-Herceptin and a ~3% increase in acidic variant for MYL-1401O 150 mg.

pH Stress:

- Following ten days of storage at acidic pH 3 at 25°C (Table 3.2.P.8.3/29):
 - No significant differences were observed in protein concentration, higher order structure by IF or secondary structure by far UV-CD for all four products.
 - Size variants: By SEC-HPLC, no significant trending was observed in HMWS content for all four products. The day 10 LMWS data indicate an increase in LMW species that is fairly consistent among products. However, the data for intermediate time points show some significant increases in LMWS; for example, at day eight, the MYL-1401O 420 mg lot increased from 0.08 to 7.13% and the 150 mg lot increased from 0.08 to 11.45%.

Reviewer comment: *The magnitude of the LMWS increase indicated by the MYL-1401O intermediate data was not seen in the US-Herceptin and EU-Herceptin lots. The LMWS increase is not consistent with the final data points or the data from the CE-SDS method. It appears more likely that this is an issue with the data, rather than an issue with the product.*

By CE-SDS non-reduced, minor increases were observed in percent Fab/HC, 2H, 2H1L, and monomer shoulder for all four products. The decrease in monomer was ~2% for all products.

- Charge variants: By IEX-HPLC, there is a small decrease in acidic variants that is part of the basic shift. An increase in basic species was observed for all four products. US-Herceptin increased ~7%, MYL-1401O 420 mg increased ~8%, EU-Herceptin increased ~8%, and MYL-1401O 150 mg increased ~9%.
- Functional assessment: No trending was observed for HER2 relative binding or FcγRIIIa binding for all four products.
- Following ten days of storage at alkaline pH 9 at 25°C (Table 3.2.P.8.3/30):

- No significant differences were observed in protein concentration, higher order structure by IF or secondary structure by far UV-CD for all four products.
- Size variants: By SEC-HPLC, minor increases in HMWS were observed for all four products.

By CE-SDS non-reduced, minor increases were observed in 2H, 2H1L, HMWS and monomer shoulder, with a minor decrease in monomer content ($\leq 2\%$) for all four molecules.

- Charge variants: By IEX-HPLC, significant increases were observed in acidic species for US-Herceptin (from 33.89 to 88.9%), MYL-1401O 420 mg (from 26.6 to 88.7%), EU-Herceptin (from 31.5 to 89.3%) and MYL-1401O 150 mg (from 29.72 to 85.45%) lots.
- Functional assessment: Consistent decreases were observed for HER2 binding for US-Herceptin (from 1.0 to 0.77), MYL-1401O 420 mg (from 0.91 to 0.85), EU-Herceptin (from 1.08 to 0.73) and MYL-1401O 150 mg (from 0.97 to 0.71) lots. There was no clear change in Fc γ RIIIa binding kinetics.

Oxidative Stress:

- Following storage for eight days in the presence of 0.1% tert-butyl hydrogen peroxide (Table 3.2.P.8.3/31):
 - Trending was observed in secondary structure by IF, where the content of beta-sheets slightly decreased and the content of beta-turns slightly increased over time for all four products. No significant differences were observed in higher order structure by IF.
 - Size variants: No significant differences or trending in HMWS was observed for all four products. By CE-SDS non-reduced, minor increases were observed in Fab/HC, 2H1L, HMWS and monomer shoulder with a minor ($\leq 1.3\%$) decrease in monomer content for all four products.
 - Charge variants: By IEX-HPLC, significant increases were observed in basic species for US-Herceptin (~ 31%), MYL-1401O 420 mg (~ 36%), EU-Herceptin (~ 31%) and MYL-1401O 150 mg (~ 38%).
 - Functional assessment: No major trending was observed in HER2 relative binding or Fc γ RIIIa binding kinetics for all four products.

Photo Stress:

- Following exposure to a maximum of 1.2 M lux hours (0.3, 0.6, 0.9, and 1.2 M lux h; Table 3.2.P.8.3/32):
 - No significant differences were observed in protein concentration or higher order structure by IF. However a minor decrease and minor increase was observed in UV-CD beta-sheets and beta-turns, respectively, for both MYL-1401O DP lots.
 - Size variants: By SEC-HPLC, increases in HMWS were observed for US-Herceptin (4.6%), MYL-1401O 420 mg (16.5%), EU-Herceptin (3.9%), MYL-1401O 150 mg (9.4%); increases in LMWS content were also observed.

By CE-SDS non-reduced, increases were observed in LC, Fab/HC, HL, fragments, 2H, 2H1L and HMWS for US-Herceptin (5.7%), MYL-1401O 420 mg (14.1%), EU-Herceptin (6.9%), MYL-1401O 150 mg (9.6%). Increases in HMWS were consistent with the increases seen using SEC-HPLC.
 - Functional assessment: Decreases in HER2 binding were significantly larger for MYL-1401O 420 mg (from 0.87 to 0.40) and MYL-1401O 150 mg (from 0.97 to 0.62) than for US-Herceptin (from 0.91 to 0.84) and EU-Herceptin (from 1.03 to 0.87). A change in FcγRIIIa binding kinetics (K_D) is not as clear, due to assay variability, but MYL-1401O 420 mg (from 103.70 to 121.93 nM) and MYL-1401O 150 mg (from 103.70 to 121.93 nM) appear to be impacted more than US-Herceptin (from 97.44 to 105.0 nM) or EU-Herceptin (from 143.30 to 144.73 nM).

Reviewer comment: Charge variants or individual degradation species, such as M255 oxidation were not evaluated. Therefore, there is not a comprehensive assessment of potential impact of light exposure or differential sensitivity to light exposure. However, both size variant assessments reveal significant degradation, and the HER2 binding assay demonstrates an impact to potency. It is not clear that the only impact to HER2 binding stems from the formation of size variants, e.g., it is not clear that the ~20% decrease in MYL-1401O monomer alone would lead to the ~50% decrease in HER2 binding activity. MYL-1401O DP lots appear more sensitive to light exposure; however, given the high intensities of light, the lack of intermediate data points for some methods (e.g., the CE-SDS assay was run only for samples exposed to 1.2 M lux h), and the limited number of lots evaluated, it is not clear that this is a true difference from US- and EU-Herceptin.

In-Use Stability

Comparative in-use stability studies were conducted on two lots of MYL-1401O 420 mg DP (batches DBBMPFV12-0001 and BS15005600) and two lots of US-Herceptin (lot 498766 and 512896). The products were reconstituted in either WFI or BWFI stored for 5 weeks at $5 \pm 3^\circ\text{C}$ and assessed by appearance, pH, protein concentration, osmolality, SEC, CE-SDS, IEX, and potency (HER2 binding) testing (Tables 3.2.P.8.3/37-40).

After 5 weeks in BWFI and WFI, the MYL-1401O lots and US-Herceptin lots showed very minor increases in LMWS, acidic variants, and basic variants (1%). MYL-1401O had larger increases in basic variants, and US-Herceptin has larger increases in acidic variants.

Reviewer comment: *The overall assessment is that there were numerous degradation pathways identified; other than size-related variants, the species associated with degradation were not identified. There were a number of instances where differences between MYL-1401O and US- or EU-Herceptin could be identified; however, it appears that these differences may be due to the extreme nature of the forced degradation conditions or the assays that were run. The stability of MYL-1401O in general will be controlled as for any product. The data collected in these studies do not preclude a conclusion of highly similar or the establishment of the analytical portion of the scientific bridges among products.*

Overall summary and conclusions of the analytical similarity assessment

Reviewer comment: *The analytical similarity assessment presented by Mylan included the pairwise evaluation of MYL-1401O and US-Herceptin, as well as the side-by-side assessment of EU-Herceptin to support establishment of the analytical portion of scientific bridges among the products, because EU-Herceptin was used in the comparative clinical studies. In addition, an analytical comparability assessment was conducted to support the use of the MYL-1401O 150 mg DP data in the evaluation of similarity. Comparability of MYL-1401O 420 mg and 150 mg DP lots was concluded.*

The analytical similarity assessment included orthogonal physicochemical, biochemical, and functional assays. Differences between US-Herceptin and MYL-1401O charge variants and glycosylation were shown. Specifically, MYL-1401O has lower levels of acidic variants compared to US-Herceptin and EU-Herceptin; MYL-1401O has lower NG-HC and terminal sialic acid content compared to US-Herceptin and EU-Herceptin; and MYL-1401O has higher total mannose content than US-Herceptin and EU-Herceptin.

Although MYL-1401O met the predetermined criteria for analytical similarity, the MYL-1401O lots had lower levels of acidic species than most lots of the lots of US-Herceptin and the majority of the lots of EU-Herceptin. The differences in acidic species among the three products correlated with variable levels of Asn30. The residual uncertainty resulting from the variability in charge is addressed in part by the equivalence in potency (HER2 binding, ADCC activity, and inhibition of proliferation) demonstrated among the three products and by the clinical safety and efficacy data. Overall, the differences in charge variants do not preclude a determination of highly similar between MYL-1401O and US-Herceptin or the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

The differences in glycosylation detected among the three products were minor; MYL-1401O met all predetermined analytical similarity criteria, except the criteria for sialic acid. Sialic acid is detected at very low levels among the three products; these levels are not likely to have clinical impact, which is supported by the clinical studies evaluating PK among the three products. Man5 content is higher in a portion of MYL-1401O lots compared to US-Herceptin and EU-Herceptin, and the levels of man6, in combination with a co-eluting glycoform, are higher in a

number of MYL-1401O lots. Given the magnitude of the differences observed, clinical impact is not expected, and the clinical data support this conclusion. Both methods used to evaluate fucosylation show similar levels of afucosylated species between US-Herceptin and MYL-1401O, although there appears to be a slightly higher trend in MYL-1401O. The levels of afucosylation in some lots of MYL-1401O and US-Herceptin were higher than those in EU-Herceptin. In addition, the MYL-1401O lots are within the US lot range for NG-HC due to an expansion of the range based on one US-Herceptin with atypically low content. However, the overall data show that MYL-1401O lots have significantly lower NG-HC content compared to both the US-Herceptin and EU-Herceptin lots. However, both the ADCC data and the FcγRIIIa binding data demonstrate statistical equivalence or similarity, respectively, among the three products. Therefore, these minor differences in glycosylation are not likely to have clinical impact. The clinical PK, safety, and efficacy data suggest that the small amount of variability in glycosylation does not have clinical impact. Therefore, the differences in the glycosylation profiles do not preclude a determination of highly similar between MYL-1401O and US-Herceptin or the establishment of the analytical portion of the scientific bridges among MYL-1401O, US-Herceptin, and EU-Herceptin.

The following table summarizes the results of the analytical similarity assessment among MYL-1401O, US-licensed Herceptin and EU-approved trastuzumab.

Quality Attribute	Method	Supports a demonstration of highly similar
Inhibition of proliferation	SKBR3 cell-based	Yes
HER2 binding	SKBR3 cell-based/Flow cytometry	Yes
ADCC	SKBR3 and PBMC cell-based	Yes
FcγRIIIa	SPR (b) (4)	Yes
FcRn	SPR	Yes
FcγRIa	SPR	Yes
FcγRIIa	SPR	Yes
FcγRIIb	SPR	Yes
FcγRIIIb	SPR	Yes
C1q	ELISA	Yes
CDC	In vitro - single assessment	Yes
Protein concentration	UV 280 nm	Yes ##
Aggregates	SEC-HPLC	Yes
	SEC-MALS	Yes
	AUC	Yes
Fragments	CE-SDS non-reducing	Yes
Charge variants	IEX-HPLC	Yes #
	cIEF	Yes #
Hydrophobic variants	HIC	Yes #
Glycation	Boronate affinity	Yes
Oxidation	Peptide mapping	Yes
Subvisible particles	MFI	Yes ##
Overall Glycosylation	NP-HPLC	Yes #
Afucosylation	RP-HPLC-LC-ESI-MS	Yes
Mannosylation	NP-HPLC	Yes #
Galactosylation	NP-HPLC	Yes
NG-HC	CE-SDS reducing	Yes #
Sialic acid	RP-HPLC	Yes #
Intact mass	LC-ESI-MS	Yes
Heavy chain mass	LC-ESI-MS	Yes
Light chain mass	LC-ESI-MS	Yes
Primary structure	LC-ESI-MS	Yes
Secondary structure	Far UV-CD	Yes
Disulfide bridging	LC-ESI-MS	Yes
Free Cysteine	Ellman's reagent	Yes
Higher order structure	Near UV-CD	Yes
	DSC	Yes
	IR	Yes
	FTIR	Yes

Differences observed in the quality attributes but the differences do not preclude a demonstration that MYL-14010 is highly similar to US-Herceptin. ## Differences due in part to the evaluation of two presentations (one non-US).

Reviewer comment: *The totality of the analytical similarity data support a conclusion that MYL-14010 is highly similar to US-licensed Herceptin, and the data provided support the establishment of the analytical portion of the scientific bridges among MYL-14010, US-Herceptin, and EU-Herceptin.*

Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Mylan evaluated the immunogenicity of MYL-14010 and EU-Herceptin in healthy volunteers (PK studies, MYL-Her-1001 and MYL-Her-1002) and metastatic breast cancer patients (confirmatory efficacy and safety study, MYL-Her-3001). The immunogenicity of MYL-14010 and EU-Herceptin was also compared to that of US-Herceptin in the PK bridging study (MYL-Her-1002) to provide further justification for the use of clinical data obtained from clinical studies using EU-Herceptin as the comparator to MYL-14010. A multi-tier approach was used to screen, confirm, and titer clinical samples for binding anti-drug antibodies (ADAs). The assay reagents were based on MYL-14010. The method and validation study for the binding antibody assay are discussed below.

***Reviewer comment:** The binding antibody assay was initially developed and validated ((b) (4) Study 8298994) for the purpose of testing the MYL-Her-1001 and MYL-Her-1002 clinical study samples. Because the PK studies were not powered to allow for meaningful conclusions to be drawn about the comparative immunogenicity of MYL-14010, EU-Herceptin, and US-Herceptin, the method validation studies for these binding antibody assays are not discussed in detail in this review. However, the assays are acceptable for use in the high level conclusions drawn from these data. The binding antibody assay discussed below was developed and validated ((b) (4) study 8289523) to test the clinical samples from study MYL-Her-3001, which was designed appropriately to allow for a determination of whether the immunogenicity incidences are similar between the products.*

During the review cycle, Mylan was requested to re-analyze the clinical immunogenicity data obtained from study MYL-Her-3001 using cut-points for binding antibody assay confirmatory and titer analyses based on more appropriate false positives rates (discussed below). Given the clinical binding ADA results (discussed below) and additional support from publicly available information regarding the incidence of ADAs to Herceptin, the review team determined that an evaluation of neutralizing ADAs was not necessary to inform for the immunogenicity assessment of MYL-14010 and US-Herceptin; therefore, the neutralizing antibody assay will not be discussed in this review.

Binding Antibody Assay Validation Report (Study 8289523)

The binding antibody assay is an electrochemiluminescence (ECL) bridging assay (IC 13-035-VI) that uses Meso Scale Discovery technology and was developed and validated for the detection, confirmation, and titration of binding ADAs directed against MYL-14010 and EU-Herceptin in human metastatic breast cancer patient serum. Samples are initially evaluated in a screening assay. Samples that test positive in the screening assay are then subjected to a confirmatory assay to demonstrate that the ADA response is specific to the drug. Confirmed ADA positive samples are then titered.

Screening Assay

Samples undergo acid dissociation to release ADA from ADA:drug complexes in the serum. Samples are then neutralized and incubated with a master mix of biotinylated and sulfo-tag labeled MYL-14010 reagents to allow MYL-14010 and EU-Herceptin specific ADAs to bind to the master mix components. After incubation, the antibody-complex bridge is added to a pre-blocked streptavidin-coated MSD plate, incubated, and washed. Read buffer containing tripropylamine is added, and the sulfo-tag reagent produces a chemiluminescent signal when

electrical voltage is applied. The signal is directly proportional to the level of binding ADAs present in the sample.

Confirmatory Assay

The confirmatory assay is run in a competitive binding format and follows the same procedure as the screening assay, except samples are incubated with an excess of MYL-1401O (500 µg/ml) during the acid dissociation procedure. Percent signal inhibition (%INH) values are calculated from the ECL counts based on the following formula:

$$\text{Percent inhibition} = 100 * [1 - (\text{response with excess drug} / \text{response with no drug})]$$

Titer Assay

The titration assay follows the same procedure as the screening assay, except samples are serially diluted in matrix prior to running of the assay. Sample titer is determined as the reciprocal of the value of the highest serial dilution that yields a response at or above the cut-point.

Matrix: Pooled normal human serum (NHS) from healthy female subjects was used to prepare the controls. Individual human Her2+ metastatic breast cancer serum samples from study MYL-Her-3001 were used for assay cut-point and selectivity assessments. A minimum required dilution of 1:40 was used for the control and test samples.

Positive Control: A rabbit anti-MYL-1401O/anti-Herceptin polyclonal antibody was used as the positive control (referred to as bulk ADA in the submission) for assay validation and clinical sample analysis (system suitability). The positive control was produced by purifying hyper-immune sera from rabbits immunized with EU-Herceptin using an affinity column prepared with MYL-1401O. Preparations of the positive control at a low concentration [20 ng/ml; low positive control (LPC)] and high concentration [1,000 ng/ml; high positive control (HPC)] were used throughout assay validation and for system suitability analysis.

Two other positive control antibodies were used during supportive validation studies (i.e., [master-mix interchangeability](#) and [antigenic equivalence](#)).

a. Rabbit anti-MYL-1401O polyclonal antibody: Produced by purifying hyper-immune sera from rabbits immunized with MYL-1401O using an affinity column prepared with MYL-1401O.

b. Rabbit anti-Herceptin polyclonal antibody: Produced by purifying hyper-immune sera from rabbits immunized with EU-Herceptin using an affinity column prepared with EU-Herceptin.

Negative Control: Pooled NHS was used as the negative control.

Critical Reagents: Critical reagents include matrix samples, positive control antibodies, biotinylated and sulfo-tagged MYL-1401O and EU-Herceptin, and unlabeled MYL-1401O and EU-Herceptin. Appendix 4 of the report includes additional information concerning the source, storage, and expiration of each critical reagent.

System Suitability: The upper limit for the negative control must not exceed 82 ECL counts (mean of NC + $t_{0.01,df}$ x SD). The LPC and HPC ranges must be within 155 and 343 ECL counts

(mean of LPC/NC ratio $\pm t_{0.05,df} \times SD$) and 6,417 and 11,775 ECL counts (mean of HPC/NC ratio $\pm t_{0.05,df} \times SD$), respectively. LPC and HPC samples and within sample replicates have %CV values $\leq 25\%$. During assay validation runs, the range of the controls was within the acceptance criteria with the exception of three LPC duplicates, which were not significantly outside the acceptable range and were associated with otherwise acceptable plates. All LPC and HPC samples and within sample replicates resulted in %CV values below 25%.

Master-Mix Interchangeability: Prior to full validation, a study was performed to determine the ability of MYL-1401O and EU-Herceptin master mixes (biotinylated and sulfo-tag reagent sets) to detect ADAs raised against each drug. The three positive controls described above were spiked in pooled NHS at 31.25, 62.50, 125, 250, 500, 1000, and 2000 ng/ml concentrations. Each positive control dilution series was evaluated in the screening assay by three analysts, and dose-response curves were generated. Each set of master-mixes can detect all three positive controls. The precision (%CV) of the mean ECL responses between the two master mixes was less than 12% and 14.9% across all runs for analysts 1 and 3, respectively. The precision of the mean ECL responses between the two master mixes for six out of seven positive control concentrations was less than 13.9% for analyst 2, which fulfills the plate acceptance criteria.

Antigenic Equivalence: Prior to full validation, a study was performed to determine the ability of each unlabeled drug to inhibit the detection of the positive controls using the labeled MYL-1401O master-mix reagents. HPC samples of the three positive controls were evaluated in the confirmatory assay using varying concentrations of unlabeled MYL-1401O and EU-Herceptin (50,000, 10,000, 3,200, 2,400, 1,600, 800, and 0 ng/ml). Three runs by three analysts were performed, and inhibition curves for each drug were generated. The HPC responses showed a comparable dose-dependent reduction with increasing concentrations of unlabeled MYL-1401O and EU-Herceptin. The precision of the mean percent inhibition values between both drugs was not greater than 13.5% CV at all drug concentrations for all three runs for each positive control with the exception of a set for which there was a preparation error.

Reviewer Comment: *The results from these studies suggest that the use of MYL-1401O-labeled reagents in the binding antibody assay results in a similar detection of ADAs against MYL-1401O and EU-Herceptin in comparison with EU-Herceptin labeled reagents.*

Assay Cut-points: Assay cut-points (Table A, below) were determined based on data derived from 48 drug-naïve, individual Her2+ metastatic breast cancer serum samples from patients enrolled in study MYL-Her-3001. Test samples were analyzed by three analysts across three plates and three days using a balanced design to minimize sources of variability.

Table A – Binding antibody assay cut-points for initial clinical sample analysis (see below regarding update to analysis)

Type of cut-point/cut-point factor	Units	False positive rate	Parametric Approach
Screening floating cut-point factor	S/N	5%	1.13
Confirmatory cut-point	% INH	0.1%	26.4%
Titer floating cut-point factor	S/N	0.01%	1.34

**Values are derived from the statistical report 2015-CP007*

Screening Cut-point

A floating cut-point approach was used to determine the screening cut-point. ECL values were provided for the assay controls and test samples. S/N ratio values were generated by dividing the mean sample ECL value by the plate-specific mean negative control ECL value for each test sample (total of 288 assay values). S/N ratio values were log-transformed and analyzed by statistical methods to assess for outliers and data distribution normality. Thirty-nine analytical and biological outliers were identified (linear mixed effects ANOVA) and were excluded from further analysis. Although tests for normality of the log-transformed S/N ratio values were not confirmed (Shapiro-Wilk, $p=0.005$), the skewness coefficient was low (0.39), indicating that the distribution was symmetric. Levene's test confirmed the homogeneity of intra-plate sample variances across plates ($p=0.5$); however, a statistical difference was observed among the assay plate mean values ($p<0.001$). A parametric floating cut-point approach based on a 5% false positive rate was used to determine the screening assay cut-point factor of 1.13 (S/N normalized ratio). The cut-point value is determined by multiplying the cut-point factor by the mean plate-specific negative control ECL value of each in-study run.

Reviewer Comment: *Sufficient data were provided to support the statistical approach used to determine the screening assay cut-point that was used to analyze the MYL-Her-3001 clinical samples. The actual false positive rate was calculated as ~4%, which supports the method used to determine the cut-point. Additionally, data were provided to show that sample mean values correlate with negative control mean values, suggesting that the negative control is appropriate for use as a normalization factor for the floating cut-point approach.*

Confirmatory Cut-point

Confirmation cut-point values were established at 1% and 0.1% false positive rates from data derived from the same samples described for the screening assay in the presence or absence of MYL-14010. The cut-point values were determined based on %INH values reported for Her2+ metastatic breast cancer samples. Percent inhibition values were analyzed by statistical methods to assess for outliers and data distribution normality; 10 outliers were excluded (linear mixed effects ANOVA) and a normal distribution of outlier-excluded data was demonstrated (Shapiro-Wilk, $p=0.671$; Figure 10, not shown). Cut-points based on parametric approaches at the 1% (mean+2.33xSD) and 0.1% (mean+3.09xSD) false positive rates were calculated as 20.8% and 26.4% INH, respectively. The parametric cut-point approach based on the 0.1% false positive rate (26.4% INH) was initially chosen to analyze the clinical samples.

Titer Cut-point

Titer floating cut-point factors were determined based on the same data and statistical methods used to establish the parametric screening floating cut-point factor. However, the titer cut-point factor was initially calculated based on a false positive rate of 0.01%. The titer cut-point factor was calculated as 1.34 and was used to analyze the MYL-Her-3001 clinical samples. Therefore, the titer for a confirmed positive sample can be determined by comparing the S/N ratio values obtained by serial dilution of the sample with the 1.34 cut-point factor. The sample titer can also be determined by comparing the ECL values of the sample serial dilutions with the negative control ECL value for the same plate multiplied by the selected cut point factor.

Reviewer Comment: *The confirmatory cut-point (i.e., 26% signal inhibition) and the titer cut-point factor (1.34) were calculated based on 0.1% and 0.01% false positive rates, respectively, which are inappropriate for analysis of the MYL-Her-3001 clinical samples. A confirmatory cut-point based on a 0.1% false positive rate may underestimate the number of patient samples with low levels of binding ADAs, and a titer cut-point factor based on a 0.01% false positive rate may increase the chance of confirmed positive samples not having a reported titer. Therefore, an information request was communicated to Mylan (05/10/2017) to (i) re-calculate the confirmatory cut-point and the titer cut-point factor based on a 1% false positive rate, (ii) re-analyze the MYL-Her-3001 clinical samples, and (iii) clearly identify any changes in ADA incidences and/or antibody titers that are a result of the re-analysis of the clinical samples.*

Mylan provided the re-analyzed binding ADA data from MYL-Her-3001 using appropriate confirmatory (20.8%) and titer cut-points (1.19 factor) based on 1% false positive rates. Sufficient data and information were provided to support the determination of these cut-points (statistical report No. 2015-007). The revised analysis of the clinical data resulted in an increase of confirmed positive ADA samples from 71 (2.5%) to 94 (3.3%); however, it was unclear how the re-analysis of the clinical samples changed the binding ADA incidences of the MYL-1401O and EU-Herceptin treatment groups with respect to baseline positivity versus treatment-induced ADA incidences. Additionally, it was noted that samples collected at “end of treatment” (defined in the clinical protocol) were not included in the immunogenicity assessment. Therefore, another information request was communicated to Mylan (05/26/2017) to update all relevant sections of the BLA to specify the updated ADA incidences for MYL-1401O- and EU-Herceptin-treated subjects (including and excluding baseline-positive patients and including end of treatment samples) based on the re-analysis of the clinical samples; Mylan provided the requested updates.

Sensitivity: The assay sensitivity was determined using data generated from the titer assay precision validation experiments. Individual log end-point titer values (3.98 – 4.54) were determined for each positive control dilution series based on the titer cut-point factor of 1.34 (0.01% false positive rate). The log end-point titer values were converted to end-point titer values (1:9550 – 1:34,674), which were converted to end-point concentration values (HPC concentration/end point titer). The mean end-point concentration of the positive control was calculated to be 2.46 ng/ml with a standard deviation of 0.79 and a CV of 32.1% (Table 24b).

Reviewer Comment: *The assay sensitivity is typically defined as the lowest concentration of the positive control antibody that tests positive in the assay or the concentration of the positive control antibody that intersects the screening cut-point on the titration curve. The sensitivity of the assay was determined based on the original titer cut-point at a 0.01% false-positive rate instead of the screening cut-point at a 5% false-positive rate or the revised titer cut-point at a 1% false positive rate. Because the determination of assay sensitivity was based on a low false positive rate, which would generate an artificially high sensitivity value, Mylan was not requested to re-calculate the sensitivity based on the updated false-positive rates. A sensitivity of 2.46 ng/ml is acceptable.*

LPC Concentration Determination: A LPC concentration of 20 ng/ml was chosen during the pre-validation exercises to yield a S/N ratio (LPC response/NC response) of approximately 3 in the screening assay, which is above the screening assay cut-point S/N factor of 1.13. The LPC generated no false negative results within the cut-point runs for the screening and confirmatory

assays, and the rejection rate was determined to be less than 0.01%, which is below the desired rejection rate of 1%.

Reviewer Comment: *It does not appear that the concentration of the LPC was determined from data obtained from the sensitivity experiment; thus, the LPC may not provide an appropriate rejection rate. Likewise, the LPC was shown to produce a ~0.01% rejection rate, which is typically not a recommended rejection rate to allow for proper assessment of assay performance near the cut-point level. However, because the assay is very sensitive (2.46 ng/ml) and the LPC provides acceptable precision (see below), it's unnecessary to lower the LPC concentration to provide an appropriate rejection rate (i.e., 1%). The use of the LPC at 20 ng/ml is acceptable to ensure the assay can detect samples with low levels of anti-drug antibodies.*

Precision: Intra-assay and inter-assay precision analyses were performed for the screening, confirmatory, and titer assays.

Screening and Confirmatory Assays

The screening and confirmatory assay precision (CV%) was evaluated in the same runs. Five duplicate sets of HPC and LPC samples, with or without drug competition (MYL-1401O and EU-Herceptin), were analyzed on each precision plate (6 runs; Table 19 – 21). For the screening assay, the intra-assay precision was NMT 17.4% CV at the LPC and NMT 6.1% CV for the HPC, and the inter-assay precision was 11.9% CV for the LPC and 13.8% CV for the HPC. For the confirmatory assay, the intra-assay precision was NMT 12.3% CV at the LPC and NMT 0.2% CV for the HPC, and the inter-assay precision was NMT 8.5% CV for the LPC and NMT 0.2% CV for the HPC.

Titer Assay

The precision for the titer assay was evaluated by serially diluting the HPC (1:40, 1:80, 1:160, 1:320, 1:640, 1:1280, 1:2560, 1:5120, 1:10240, 1:20,480, 1:40,960, and 1:81,920 dilutions) across the titer assay cut-point. Each dilution was analyzed in triplicates across four runs. The ECL values from each dilution series were analyzed to determine the log end point titer values. The mean log end point titer was determined to be 4.23. The intra-assay precision of the titer assay results (i.e., log end-point titer) was less than 3.9% CV for each of the four titer assay runs (Table 24b). The inter-assay precision of the titer assay results was 3.3% CV. In addition, all titration series had log end-point titer values within the mean log end-point titer $\pm$ log2, which is a plate criterion for this parameter.

Based on the end-point titer calculations from the precision data, a minimum significant ratio of 3 was calculated (Table 24b); therefore, a change in titer of more than 3-fold was considered to indicate a statistically significant increase or decrease in sample titer.

Prozone Effect: The assay is able to detect the HPC (1,000 ng/ml). To determine whether higher concentrations of antibodies interfere with the screening assay performance to produce false negatives (i.e., prozone effect), samples with concentrations of the positive control antibody above the HPC level (i.e., 50,000 ng/ml and 10,000 ng/ml) were evaluated in the assay. Samples with 50,000 ng/ml and 10,000 ng/ml of the positive control antibody produced ECL counts of 803,013 and 89,262, respectively, which are above the ECL counts for the plate-specific cut-point (83 counts) and the HPC (~8,500 counts).

Reviewer Comment: *The data suggest that there is no prozone effect observed in the assay with ADA concentrations as high as 50,000 ng/ml; there is acceptable correlation with ADA concentrations and ECL counts ($r=0.999$). It is likely that samples with very high concentrations of ADAs will not impact assay performance.*

Specificity: An irrelevant antibody (rabbit anti-BMO-2) was used to spike matrix samples at the LPC (20 ng/ml) and HPC (1,000 ng/ml) levels. These samples produced ECL counts (61 and 64) below the plate-specific cut-point (73 counts). Additionally, a non-specific drug (BMO-2) was used in the confirmatory step for analysis of LPC and HPC samples prepared with the positive control antibody. The positive control samples were confirmed to be positive when analyzed with excess MYL-1401O drug (99.3% INH, HPC; 76% INH, LPC) but not with excess BMO-2 (1% INH, HPC; 1.2% INH, LPC).

Reviewer Comment: *Although EU-Herceptin wasn't used in the confirmatory step, data from the antigenic equivalence experiment demonstrate that unlabeled EU-Herceptin and MYL-1401O inhibit ADA responses at a comparable level with comparable precision.*

Selectivity: Fifteen individual pre-dosed patient Her2+ metastatic breast cancer serum samples from the MYL-Her-3001 clinical study were spiked with the positive control antibody (LPC level of 20 ng/ml) or left untreated. All of the individual samples spiked with the positive control antibody exhibited a positive result from screening (231– 304 ECL counts) and confirmatory (77-80% INH; cut-point = 26.4%) analyses (Table 27). The LPC samples produced screening and confirmatory assay responses between 249 – 259 ECL counts and 73.9 – 77.5% INH, respectively.

The potential for lipaemic or haemolysis interference was also evaluated in the screening and confirmatory assays using five individual NHS samples. All lipaemic (30 mg/dL of triglycerides) and haemolysed (70-250 mg/dL haemoglobin) samples spiked with the positive control antibody (LPC level) exhibited a positive assay response in both screening and confirmatory assays (Table 33), while all unspiked lipaemic and haemolysed individual samples exhibited negative assay responses.

Her2-ECD Interference: Circulating levels of the extracellular domain of Her2 (Her2-ECD) are present in the serum of Her2+ metastatic breast cancer patients. Normal levels of Her2-ECD are around 15 ng/ml, but levels are elevated in Her2+ metastatic breast cancer patients. Interference of assay performance was evaluated by using Her2+ metastatic breast cancer patient serum samples (sourced from MYL-Her-3001 clinical study and (b)(4) with varying concentrations of Her2-ECD (63 – 1,470 ng/ml). A total of 8 out of the 10 samples tested positive during the screening assay, and 5 out of the 8 screened positive samples were confirmed to be positive (Table 34). The samples that were confirmed positives consisted of Her2-ECD concentrations ≥ 720.56 ng/ml (720 – 1,470 ng/ml), with the exception of a sample with a Her2-ECD concentration of 228.50 ng/ml.

Reviewer Comment: *The data provided indicate that high concentrations of Her2-ECD have the potential to generate false positive ADA responses. Only ~4% of patients enrolled in MYL-Her-*

3001 showed Her2-ECD concentrations above 228.50 ng/ml (~114/2910; Table 4, (b) (4) study 8286511), and the incidence of ADA generation in the patient population was very low, suggesting that interference from high Her2-ECD concentrations in clinical samples is minimal.

Drug Interference: An experiment was performed to determine the highest amount of MYL-1401O that can be added to a matrix sample containing the positive control antibody (31.25 – 2,000 ng/ml) without interfering with the ability of the assay to detect a positive assay response. Samples with MYL-1401O (100 – 175 µg/ml) and the positive control (31.25 – 2,000 ng/ml) led to positive assay responses (Table 26).

Reviewer Comment: *The data demonstrate that the assay can detect ADAs as low as 31.25 ng/ml without interference from 100 to 175 µg/ml of MYL-1401O. The drug tolerance limits for MYL-1401O are at or above the highest limit of drug trough levels (2 – 175 µg/ml). This assay appears to be able to tolerate on-board levels of MYL-1401O relevant to the current clinical study.*

Stability: The stability of the HPC and LPC was evaluated by comparing freshly prepared controls to controls (i) subjected to up to 6 freeze thaw cycles at -20°C and -80°C and (ii) stored at room temperature for 24 and 48 hours. The mean responses of the LPC and HPC samples after 2, 4 and 6 freeze thaw cycles at -20°C and -80°C were within 12.6% of the mean responses observed for the baseline LPC and HPC samples. The mean responses of the LPC and HPC samples after storage at room temperature for 24 and 48 hours were within 4.3% of the mean responses observed for the baseline LPC and HPC samples.

Reviewer Comment: *The data provided suggest that clinical serum samples are likely to be stable for up to 6 freeze thaw cycles and 48 hours at room temperature. Additional stability data for long-term storage of the positive control were not provided for this assay; however, long-term stability data collected for the previous version of the assays were provided. The data from these studies demonstrate that the ADAs spiked in NHS and Her2+ metastatic breast cancer serum were stable for ~6 months when stored at -20°C and ~23 months when stored at -80°C ((b) (4) Study 8264133).*

Sufficient information and data were provided to support the suitability of the binding antibody assay to analyze the MYL-Her-3001 serum samples.

MYL-Her-3001 serum sample analysis for the detection of binding ADAs (Study 8255251)

MYL-Her-3001 is a multicenter, double-blind, randomized, parallel-group study comparing the efficacy and safety of MYL-1401O versus EU-Herceptin in patients with Her2+ metastatic breast cancer. The immunogenicity of MYL-1401O and EU-Herceptin was assessed by analyzing samples collected at baseline (week 0) and at weeks 6, 12, 18, 24, 36, and 48. Additionally, samples were collected at end of treatment as defined in the clinical protocol. The overall binding ADA incidences (positive result at least once post-baseline) were calculated as 5.9% (14 out of 247 patients) and 6.8% (16 out of 246 patients) for MYL-1401O- and EU-Herceptin-treated subjects, respectively. The treatment-induced ADA incidences (baseline negative patients who tested positive at least once at any time-point post-baseline) were calculated as 3.2% (7 out of 222 patients) and 3.3% (7 out of 210 patients) for MYL-1401O- and EU-Herceptin-treated

subjects, respectively. Post-dose ADA end-point titers in both treatment groups were comparable and generally low.

Reviewer Comment: *The clinical study data indicate that the assay performed acceptably during clinical sample analysis. Although Mylan did not factor the MRD into the calculation of antibody titers, as recommended by FDA guidance, this would not change the comparative immunogenicity assessment.*



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

Date: 10/5/2017
To: Administrative File, STN 761074
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for Ogivri® (MYL-1401O)
US License: 2062
Applicant: Mylan GmbH
Mfg Facility: Drug Substance:

[Redacted] (b) (4)

Drug Product:
[Redacted] (b) (4)

Product: Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab)
Dosage: Sterile, preservative-free lyophilized powder for intravenous infusion that is supplied as a multi-use vial containing 440 mg of MYL-1401O, intended for reconstitution with 20 mL of the appropriate diluent, BWFI (supplied) or SWFI (not supplied) to yield a solution containing 21 mg/mL Drug Product.
Indication: Therapeutic for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.
Due Date: 01/03/2018

RECOMMENDATION: This application is recommended as approve from a facility review perspective.

For the proposed drug substance and drug product manufacturing site, two inspections were recently conducted for [Redacted] (b) (4) a PLI from [Redacted] (b) (4) and a surveillance inspection from [Redacted] (b) (4). Observations from both inspections were reviewed to consider potential impact to the proposed operations for Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) drug product manufacturing. Corrective actions from the PLI conducted from [Redacted] (b) (4) were completed and deemed adequate.

Corrective actions from the surveillance inspection conducted from [Redacted] (b) (4) were completed and deemed adequate. [Redacted] (b) (4) proposed 59 CAPAs, including the [Redacted] (b) (4). An update from the firm received September 15, 2017 stated that 28 CAPAs are still outstanding. Some of the outstanding CAPAs

BLA 761074/0. Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) DS and DP Manufacture

are critical to confirming [REDACTED] (b) (4) In the CAPA status update, the firm stated that [REDACTED] (b) (4)

[REDACTED] (b) (4) Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) is proposed [REDACTED] (b) (4) All critical CAPAs are have been addressed and the firm is currently ready to manufacture. BLA 761074 for manufacture of Ogivri® (MYL-1401O, a proposed biosimilar to Trastuzumab) is **recommended for approval**.

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CONCLUSION

Adequate descriptions were provided for the (b) (4) Ogivri® (MYL-1401O) Drug Substance and Drug Product facility proposed for DS and DP manufacture. :

- (b) (4)

The proposed drug substance and drug product manufacturing ((b) (4)) is currently **recommended for approval** from a facilities assessment standpoint.

Michael R.
Shanks -S
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Shanks -S
DN: cn=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
ou=2342.19200300.100.1.1=2001-00
8317, cn=Michael R. Shanks -S
Date: 2017.11.15 13:26:40 -05'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: August 10, 2017
To: Administrative File, STN 761074\0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 2062
Applicant: Mylan GmbH
Facility: (b) (4)
Product: MYL-1401O, Ogivri ((proposed biosimilar to Herceptin® trastuzumab),
Dosage: Lyophilized powder (440mg) in a multi-use vial for intravenous infusion
Indication: For the treatment of HER2 overexpressing breast cancer, metastatic gastric cancer or gastroesophageal junction adenocarcinoma
Due Date: September 03, 2017

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY: Mylan GmbH submitted a 351(k) application, BLA 761074 to license MYL-1401O, a proposed biosimilar to Herceptin® for the following indications: HER2 overexpressing breast cancer, metastatic gastric cancer or gastroesophageal junction adenocarcinoma. (b) (4)

the lyophilized drug product are manufactured by (U) (S).

The application was submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2 - Cover letter, and Module 2 Module 3, appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), regional section (3.2.R) and literature references (3.3).

Letter of authorization (LOA) (b) (4)
were provided.

INTRODUCTION:

MYL-1401O is a proposed biosimilar to Herceptin® for the following indications: HER2 overexpressing breast cancer, metastatic gastric cancer or gastroesophageal junction adenocarcinoma. MYL-1401O (DP) is a sterile, preservative-free lyophilized powder for intravenous infusion. Each vial of DP is co-packed with a vial containing 20 mL of BWFI

containing 1.1% benzyl alcohol as a preservative. [REDACTED] (b) (4)
 [REDACTED] are manufactured by [REDACTED] (b) (4)

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	November 03, 2016	Original
0006	December 19, 2016	Amendment for shipping
0008	December 21, 2016	Response to IR
0009	January 03, 2017	Response to IR
0015	January 23, 2017	Response to IR
0024	April 24, 2017	Response to IR
0026	May 08, 2017	Response to IR
0043	July 26, 2017	Response to IR
0046	August 04, 2017	Response to IR

ASSESSMENTS:

3.2.P DRUG PRODUCT

Reviewer's comment: There are two sections of 3.2.P, one for the lyophilized presentation of the DP and the other for the BWFI used for reconstituting the lyophilized drug product.

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

Bacteriostatic Water for Injection (BWFI), USP (1.1% Benzyl Alcohol)

BWFI is sterile WFI containing 1.1% of benzyl alcohol as preservative. Twenty mL of BWFI is supplied in a vial for the reconstitution of DP to yield a multi-dose solution containing 21 mg/mL DP, pH 6.0.

Satisfactory

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

3.2.P.2.3 Manufacturing Process Development

(b) (4)



Satisfactory

3.2.P.2.5 Microbiological Attributes

Sterility and endotoxin testing is performed on BWFI as part of batch release and stability testing.

ANTIMICROBIAL EFFECTIVENESS TEST (AET)

The DP reconstituted with BWFI can be stored for up to 28 days at 2-8°C. The effectiveness of the antimicrobial property of the benzyl alcohol in BWFI was demonstrated using a development batch containing lower strength of 0.9% benzyl alcohol and 3 PV batches with label claim strength of 1.1% benzyl alcohol as per USP <51>. The results of this study presented in Table 3.2.P.2.5/ 1 - Table 3.2.P.2.5/ 4 of the submission demonstrated the bacteriostatic and fungistatic effectiveness of BWFI for both benzyl alcohol concentrations for up to 28 days at 20- 25°C. Eight log reduction of challenged organisms was observed after 7 days and no growth was after 14 and 28 days of incubation. All the media used for AET passed growth promotion.

The antimicrobial effectiveness of post reconstituted DP with BWFI at 0.9% concentration (80% concentration of the label claim of 1.1% BWFI) was reviewed in section 3.2.P.3.5 of DP.

Reviewer's comment: The applicant in amendment dated April 24, 2017 in sequence # 0024 submitted protocol and report for the Preservative Efficacy Test for BWFI. The report also included data for the suitability testing study performed to demonstrate recovery of the challenge microorganisms after neutralization of BWFI. BWFI batches challenged with Pseudomonas aeruginosa, Staphylococcus aureus, E.coli, Candida albicans, and Aspergillus brasiliensis were neutralized using Dey-Engley neutralizing broth (DEB). After 1 min, 5 min, and 10 hold with DEB, the recovery of challenge microorganisms were evaluated. The results of the suitability testing study summarized in Table 1 and Table 2 of the report indicated that the recovery of challenge microorganisms was >75% for all tested time points for the BWFI batches. Media used for this study passed growth promotion testing.

Satisfactory

SEAL INTEGRITY OF THE CONTAINER CLOSURE

Both microbial ingress test and dye ingress test were used to evaluate the integrity of the container closure system of the media filled and BWFI filled vials. The description of microbial and dye ingress test methods are provided in section 3.2. P.3.5 is reviewed here.

Microbial Ingress Test

Twenty media filled vials were used for microbial ingress CCI testing. Positive controls are prepared by pricking the closures 10 times using a sterile needle and pre-incubated. A vial which passed sterility testing served as negative control. Positive and test units were immersed in TSB media inoculated with *Brevundimonas diminuta* and exposed to vacuum pressure of 27 kPa for 30 minutes. After completion of the 14 days of incubation the test and negative vials subjected for the growth promotion test.

The acceptance criteria are test and negative control vials and should not show any growth at the end of the 14 days. The positive controls should show growth within 3 days of incubation. The vials subjected to GPT of *B.diminuta* should show growth within 3 days.

Dye Ingress Test

Five BWFI vials were used for dye ingress CCI testing. Positive controls are prepared by pricking the closures 10 times using a sterile hypodermic needle. Positive units immersed in 0.1% w/v of methylene blue and exposed to 25-30 kPa for 10 min followed by 30 minutes of atmospheric pressure. Vials were checked for any trace of dye by comparing with an unexposed vial from the same batch on white background.

The dye ingress method is used for testing CCI during stability program. Sterility testing and CCIT using dye ingress test will be performed annually and at the end of shelf life.

Reviewer's comments: CCI test method is not adequate because compromised vials with defined breach size are not included. An information request was sent on December 16, 2016 to clarify and provide additional details on qualification of microbial immersion and dye ingress CCI test methods.

The applicant in amendment dated January 03, 2017 in sequence # 0009 confirmed that vials used for qualification of microbial immersion and dye ingress CCI test methods are the same as the commercial vials described in BLA Section 3.2.P.7. Protocol and reports for BWFI Microbial Ingress CCIT were provided. The microbial immersion test was performed with a breach size of 800 µm under vacuum pressure of 27 kPa for 30 minutes.

Mylan submitted the re-qualification report for the dye ingress CCIT method for BWFI container closure system in amendment dated January 23, 2017 in sequence # 0015. Three BWFI lots, BS15009391, BS15009392 and BS15009393 were used for this study. The study included a compromised positive control with a breach size of 20 µm and 10 vials pierced 10 times with 21G needle exposed to the test conditions listed in the table reproduced below and an unexposed non compromised negative control. The limit of detection (LOD) for visible analysis of the test samples is ^(b)₍₄₎ppm of the dye in solution.

Parameters/criteria	Values/Limits
Concentration of methylene blue	0.1% w/v
Number of vials	10 vials
Number of piercing per unit	10 times
Vacuum pressure	25-30 kPa
Pressure hold time	10 min
Number of Negative control	1
Number of positive control with breach size of 20 µm using capillary tube	1
Acceptance criteria for product	None of the containers should show evidence of coloured solution
Acceptance criteria for positive control	The positive control should show blue colour.
Acceptance criteria for negative control	No colour in the negative control.

All acceptance criteria were met. Vials pierced 10 times with 21G needle did not produce any color demonstrating the self-sealing of the container closure. Routine CCI testing will be performed using the qualified parameters including positive control vial with 20 µm breach size and the dye ingress will be detected visually by comparing the samples exposed to the dye solution with those not exposed to dye solution (negative control).

The applicant also proposed to requalify the current microbial immersion test method to demonstrate the method sensitivity/capability to detect the smaller breach size from a microbiological perspective. This was not followed up as the requalified dye ingress method is capable of detecting 20µm breaches in the CCS.

Satisfactory

3.2.P.3.1. MANUFACTURER(S)

Facility:

[REDACTED] (b) (4)

Responsibilities

[REDACTED] (b) (4)

Reviewer comments:

A pre-license inspection (PLI) of [REDACTED] (b) (4) was performed from [REDACTED] (b) (4) [REDACTED] FDA 483 form with 8-observations was issued with the initial VAI classification of the facility. Refer to Panorama for the updated status of this facility.

3.2.P.3.2. BATCH FORMULA

The batch size of BWFI is [REDACTED] (b) (4) L and it corresponds to approximately [REDACTED] (b) (4) vials.

3.2.P.3.3. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

The equipment used during the manufacturing process of BWFI listed in Table 3.2.P.3.3/ 2 is reproduced below.

Satisfactory

3.2.P.8 STABILITY

Six months of long-term stability data at $5 \pm 3^{\circ}\text{C}$ and accelerated ($25 \pm 2^{\circ}\text{C}$, 60% RH $\pm$ 5% RH) for 3 PV batches, 36 months supportive stability data at $5 \pm 3^{\circ}\text{C}$ and 6 months data at accelerated and stressed conditions ($40 \pm 2^{\circ}\text{C}$, 75% RH $\pm$ 5% RH) for 3 batches of DP manufactured by Process B and comparative forced degradation studies at lyophilized state and liquid state of DP with Herceptin® from the US and EU source were provided. Based on these data, a ^(b)₍₄₎-month shelf life is proposed for DP at $5 \pm 3^{\circ}\text{C}$. Sterility, endotoxin were tested initially and annually until expiry for the batches in long-term storage at $5 \pm 3^{\circ}\text{C}$. Additionally, CCIT was implemented annually until expiry starting the PV batches in the long term stability protocol. All batches met the acceptance criteria for sterility, endotoxin for the tested time points.

Post-Approval Stability Protocol and Stability Commitment

Applicant commits to complete the ongoing studies and will also place one batch of DP annually at long-term storage conditions of $5 \pm 3^{\circ}\text{C}$. In the post approval stability program microbiological tests (endotoxin, sterility, and CCI) are performed annually until expiry.

Reviewer's comments: Mylan in amendment dated June 23, 2017 in sequence # 0037 updated section 3.2.P.8 with 12 month real time stability data for 3 PV batches. The applicant in amendment dated July 26, 2017 in sequence # 0043 updated section 3.2.P.8 with 48 month real time stability data from 3 batches of DP manufactured by Process B. Sterility and endotoxin at the tested time points met acceptance criteria.

Satisfactory

Conclusion

- I. The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective
- II. Product quality aspects other than microbiology are deferred to the OBP reviewer.
- III. See Panorama for the compliance status of the drug product manufacturing site.



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Narasimhan

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LABELS AND LABELING REVIEW

Date:	July 31, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Kristen Nickens, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761074
Product:	Ogivri (trastuzumab-dkst)
Applicant:	Mylan GmbH
Submission Date(s):	November 3, 2016, January 26, 2017, May 16, 2017, May 24, 2017, June 16, 2017, June 28, 2017, July 7, 2017, and July 24, 2017

I) RECOMMENDATION

The labels and labeling for Ogivri (trastuzumab-dkst) for Injection, 420 mg/vial multiple-dose vial submitted on July 24, 2017 are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant, Mylan GmbH, submitted BLA 761074 Ogivri (trastuzumab-dkst) on November 3, 2016 as a proposed biosimilar to US-licensed Herceptin (trastuzumab).

Table 1 presents relevant product information for trastuzumab-dkst and US-licensed Herceptin.

Table 1. Relevant Product Information for the proposed biosimilar product and US-licensed Herceptin		
Product	Proposed Biosimilar	US-licensed Herceptin
Proprietary Name:	Ogivri	Herceptin
Nonproprietary Name:	trastuzumab-dkst	trastuzumab
Dosage Form:	for injection	for injection
Strength and Container-Closure:	420 mg/vial (multiple dose)	420 mg/vial (multiple dose) 150 mg/vial (single dose)
Route of Administration:	intravenous infusion	
Storage and Handling:	Vial stored in refrigerator at 2° to 8°C (36° to 46°F) until time of reconstitution	
Indication:	Adjuvant HER2 overexpressing breast cancer Metastatic HER2 overexpressing breast cancer Metastatic HER2 overexpressing gastric cancer (US-licensed Herceptin only: the gastric cancer indication is protected by orphan drug exclusivity expiring on October 20, 2017)	
Dose and Frequency:	Adjuvant HER2 overexpressing breast cancer Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes	

	weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin). One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks. Or as a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes. Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks. <u>Metastatic HER2 overexpressing breast cancer</u> Initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions. <u>Metastatic HER2 overexpressing gastric cancer (US-licensed Herceptin only, see statement above)</u> Initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

III) MATERIALS REVIEWED

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

Table 1: Materials Considered for this Label and Labeling Review

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

n/a = not applicable for this review

IV) DISCUSSION

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

V) CONCLUSION

The labels and labeling for Ogivri (trastuzumab-dkst) for injection, 420 mg/vial multiple-dose vial were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57;

21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on July 24, 2017 are acceptable from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling (submitted May 24, 2017)

Prescribing Information ([Application 761074 - Sequence 0031 - Draft Labeling Text Marked Up Word](#))

Container Labels (submitted May 16, 2017)



Carton Labeling (submitted May 16, 2017)

Appendix B: Other (N/A)

Appendix C: Relevant CFR and CDER Best Labeling Practices

Table 2: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Proper Name</u> 21 CFR 610.60 21 CFR 201.50 21CFR 201.10		x		See conditionally acceptable suffix per DMEPA ⁵ . Consider adding the dosage form "For Injection" to appear underneath the proper name as follows: Ogivri (trastuzumab-xxxx) For Injection 420 mg/vial <i>Applicant's revision is acceptable</i>
<u>Manufacturer name, address, and license number</u> 21 CFR 610.60		x		Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h and includes a placeholder for the US license No. Revise from [REDACTED] (b) (4) to appear as follows per 21 CFR 610.60 (a)(2): Manufactured by: Mylan GmbH Zurich, Switzerland CH-8050 US License No. xxxx <i>Applicant revised the manufacturer name and address as requested. They also added distributor statement. We find this revision acceptable since the applicant has fulfilled the requirement for 21 CFR 610.60 (a)(2).</i> <i>The applicant added [REDACTED] (b) (4) India' to maintain consistency with Mylan's current standard format.</i>

¹ Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Gao T. Nonproprietary name suffix memorandum. RCM # 2017-1078 BLA 761074. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 June 30. P4.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				The Applicant may include the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11. However, consider revising the country of origin labeling statement to appear as "Product of India" <i>Applicant's revision is acceptable</i>
<u>Lot number or other lot identification</u> 21 CFR 610.60 21 CFR 201.18 21CFR 201.100	x			
<u>Expiration date</u> 21 CFR 610.60 21 CFR 201.17	x			
<u>Multiple dose containers</u> 21 CFR 610.60	x			Revise the usual dose statement from "See (b) (4) prescribing information for (b) (4) and administration." to read "See prescribing information for dosage, preparation, and administration." <i>Applicant's revision is acceptable</i>
<u>Statement: "Rx only"</u> 21 CFR 610.60 21 CFR 201.100	x			Consider relocating the "Rx only" statement to appear in the upper right corner of the principal display panel to allow space for other important information such as the route of administration statement. <i>Applicant's revision is acceptable</i> Consider placing the route of administration to appear above the package type term (Multiple-Dose Vial). <i>Applicant's revision is acceptable</i>
<u>Medication Guide</u> 21 CFR 610.60			x	
<u>No Package for container</u> 21 CFR 610.60			x	
<u>Partial label</u>			x	

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.60 21 CFR 201.10				
<i>No container label</i> 21 CFR 610.60 (d)			x	
<i>Visual inspection</i> 21 CFR 610.60	x			Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the container to allow for visual area of inspection of the contents. <i>Applicant confirms that the label gap as 14mm on the Ogivri vial and 19 mm on the BWFI vial. We find this acceptable.</i>
<u>NDC numbers</u> 21 CFR 201.2 21CFR 207.35	x			
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100		x		Relocate the route of administration statement to appear on the principal display panel underneath the strength statement and revise to read as follows: "For intravenous infusion after reconstitution" per 21 CFR 201.5 (f). <i>Applicant's revision is acceptable</i>
<u>Preparation instructions</u> 21 CFR 201.5		x		Revise the preparation instructions from "Reconstitute with 20 mL Bacteriostatic Water for Injection (BWFI), USP (1.1% benzyl alcohol) to yield a multiple-dose solution containing approximately 21 mg/mL trastuzumab at a pH of approximately 6." to read "Reconstitute with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, (1.1% benzyl alcohol) to yield a multiple-dose solution containing 21 mg/mL trastuzumab-xxxx that delivers x mL (x mg). Do Not Shake. Store reconstituted solution in refrigerator at 2°C to 8°C (36°F to 46°F). Do not Freeze. Discard unused reconstituted solution after 28 days." to include the deliverable volume of the reconstituted solution, directions for proper storage of the constituted solution, and an expiration or beyond-use date per USP General Chapters: <7> Labeling in the same visual field.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				<i>Applicant's revision is acceptable</i> Consider revising the statement (b) (4) " to read: "Discard after ___/___/___." for clarity. Note that the Herceptin vial has "do not use after" <i>Applicant's revision is acceptable</i>
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs</u> <u>Misleading</u> <u>statements</u> 21 CFR 201.6	x			
<u>Strength</u> 21 CFR 201.10 21CFR 201.100		x		Revise the strength statement from "(b) (4) mg" to read "420 mg per vial" per 21 CFR 201.10 (d) and per Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 421- 424). <i>Applicant's revision is acceptable</i>
<u>Drugs</u> <u>Prominence of</u> <u>required label</u> <u>statements</u> 21 CFR 201.15		x		Reduce the prominence of the pink swirl graphic per 201.15(b)(1). <i>Applicant's revision is acceptable</i>
<u>Bar code label</u> <u>requirements</u> 21 CFR 201.25 21CFR 610.67	x			
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage</u> <u>statement</u> 21 CFR 201.55 21CFR 201.100	x			See recommendation for multiple dose vial above.
<u>Inactive ingredients</u> 21 CFR 201.100			x	Although this is not considered a partial label, the container label lacks sufficient space for this information, thus this information must appear on the carton, PI, and IFU (if applicable). See carton

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				recommendations below.
<u>Storage requirements</u>	x			Remove the following sentence from the storage statement: (b) (4) (b) (4) (b) (4) (b) (4) since this information will be included in the reconstitution statement. Revise the storage statement from "(b) (4)" to read " Store in refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution" for consistency with language in the prescribing information. Consider relocating the storage statement to appear before the reconstitution statement to coincide with the order of stages of use. <i>Applicant's revision is acceptable</i>
<u>Dispensing container</u> 21 CFR 201.100			x	
<u>USP monograph for Bacteriostatic Water for Injection, USP vial</u>	x			Packaging and Storage: Preserve in single-dose or multiple-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass, of not larger than 30-mL size. Labeling: Label it to indicate the name(s) and proportion(s) of the added antimicrobial agent(s). Label it also to include the statement "Not For Use In Newborns", in boldface capital letters on the label immediately under the official name, printed in a contrasting color, preferably red. Alternatively, the statement may be placed prominently elsewhere on the label if the statement is enclosed within a box. Relocate the statement "(pH 4.5 to 7.0)" to appear on the side panel so that the statement "NOT FOR USE IN NEWBORNS" appears directly beneath the official name per the USP monograph labeling requirements. <i>Applicant's revision is acceptable</i> Relocate the following statement to appear on the side panel and revise from: (b) (4)

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				(b) (4) to read "Use 20 mL as DILUENT for reconstitution of Ogivri" with only the word "diluent" in all caps so that it appears more prominent. <i>Applicant's revision is acceptable</i> Add the statement "For Drug Diluent Use Only" to appear in any color other than red and on the principal display panel underneath the "NOT FOR USE IN NEWBORNS" statement <i>Applicant's revision is acceptable</i> Ensure that the correct format of the qualifying phrase for the distributor of Bacteriostatic Water for Injection, USP vial appears on its label per 21 CFR 201.1(h)(5) and revise accordingly as follows: Manufactured by Biocon Limited Bangalore, India for Mylan (b) (4) Applicant revised as requested however, we request that you revise the manufacturer/distributor statement for the Bacteriostatic Water for Injection, USP vial label to comply with OBP preference that lists the BLA Applicant with the Switzerland address as follows: Manufactured by Biocon Limited Bangalore, India for Mylan GmbH Zurich Switzerland CH-8050 <i>Applicant's revision is acceptable</i>

Package Label⁶ Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21CFR 610.61 21 CFR 201.50 21CFR 201.10	x			See conditionally acceptable suffix per DMEPA ⁷ to be added to all final labels and labeling. Consider adding the dosage form "For Injection" to appear underneath the proper name on all panels as follows: Ogivri (trastuzumab-xxxx) For Injection <i>Applicant's revision is acceptable</i>
<u>Manufacturer name, address, and license number</u> 21CFR 610.61(b)				Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h and includes a placeholder for the US license No. Revise from [REDACTED] ^{(b) (4)} to appear as follows per 21 CFR 610.61 (b): Manufactured by: Mylan GmbH Zurich, Switzerland CH-8050 US License No. xxxx <i>Applicant's revision is acceptable</i>
<u>Lot number or other lot identification</u> 21CFR 610.61 (c)	x			
<u>Expiration date</u> 21CFR 610.61 (d) 21 CFR 201.17 (Location)	x			
<u>Preservative</u> 21 CFR 610.61 (e)		x		Add the statement "No preservative" to appear on the principal display panel per 21 CFR 610.61 (e). <i>Applicants revision is acceptable</i>

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

⁷ Gao T. Nonproprietary name suffix memorandum. RCM # 2017-1078 BLA 761074. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 June 30. P4.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Number of containers</u> 21CFR 610.61 (f)	x			Remove the statement [redacted] (b) (4) from the principal display panel to permit space for other important information such as the route of administration ("For intravenous infusion after reconstitution".) and the [redacted] (b) (4). <i>Applicant's revision is acceptable</i> Revise the contents statement from: "Contents: Each carton contains one preservative-free 420 mg vial of Ogivri [redacted] (b) (4) and one vial containing 20 mL of Bacteriostatic Water for Injection, USP (1.1% benzyl alcohol)." to read as follows: "Contents: Each carton contains one 420 mg vial of Ogivri and one vial containing 20 mL of Bacteriostatic Water for Injection, USP (1.1% benzyl alcohol)." <i>Applicant's revision is acceptable</i>
<u>Strength/volume</u> 21CFR 610.61 (g) 21 CFR 201.10 (d) 21CFR 201.100 (b)(4)		x		Revise the strength statement from "[redacted] (b) (4) mg" to read "420 mg per vial" per 21CFR 610.61 (g), 21 CFR 201.10 (d) and per Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 421- 424). <i>Applicant's revision is acceptable</i>
<u>Storage temperature</u> 21CFR 610.61 (h)	x			Remove the following sentence from the storage statement: [redacted] (b) (4). [redacted] since this information will be included in the reconstitution statement. Revise the storage statement from "[redacted] (b) (4) [redacted]." to read "Store in refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution" for consistency with language in the prescribing information. Consider relocating the storage statement to appear before the reconstitution statement to

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				coincide with the order of stages of use. <i>Applicant's revision is acceptable</i>
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 21CFR 610.61 (i)	x			see recommendation for preparation instructions
<u>Multiple dose containers</u> 21CFR 610.61	x			Revise the usual dose statement from "See (b) (4) prescribing information for (b) (4) and administration." to read "See prescribing information for dosage, preparation, and administration." <i>Applicant's revision is acceptable</i>
<u>Route of administration</u> 21 CFR 610.61	x			Relocate the route of administration statement to appear on the principal display panel underneath the strength statement and revise to read as follows: "For intravenous infusion after reconstitution" per 21 CFR 201.5 (f). <i>Applicant's revision is acceptable</i>
<u>Known sensitizing substances</u> 21CFR 610.61 (l)			x	
<u>Antibiotics added during manufacturing</u> 21CFR 610.61 (m)			x	
<u>Inactive ingredients</u> 21CFR 610.61 21 CFR 201.100	x			Revise the Inactive ingredients list to appear in alphabetical order per USP <1091> Labeling of Inactive Ingredients. <i>Applicant's revision is acceptable</i>
<u>Adjuvant, if present</u> 21CFR 610.61			x	
<u>Source of the product</u> 21CFR 610.61			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Identity of each microorganism used in manufacturing</u> 21CFR 610.61	x			
<u>Minimum potency of product</u> 21CFR 610.61	x			
<u>Rx only</u> 21CFR 610.61	x			
<u>Divided manufacturing</u> 21 CFR 610.63			x	
<u>Distributor</u> 21 CFR 610.64	x			<i>Applicant revised the manufacturer name and address as requested. They also added distributor statement. We find this revision acceptable since the applicant has fulfilled the requirement for 21 CFR 610.60 (a)(2).</i> <i>The applicant added (b) (4) India' to maintain consistency with Mylan's current standard format.</i> The Applicant may include the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11. However, consider revising the country of origin labeling statement to appear as "Product of India" <i>Applicant's revision is acceptable</i>
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	x			
<u>NDC numbers</u> 21 CFR 201.2	x			
<u>Preparation instructions</u> 21 CFR 201.5	x			Revise the preparation instructions from "Reconstitute with 20 mL Bacteriostatic Water for Injection (BWFI), USP (1.1% benzyl alcohol) to yield a multiple-dose solution containing approximately 21 mg/mL trastuzumab (b) (4) to read "Reconstitute with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, (1.1% benzyl alcohol) to yield a multiple-dose solution containing 21 mg/mL

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				trastuzumab-xxxx that delivers x mL (x mg). Do Not Shake. Store reconstituted solution in refrigerator at 2°C to 8°C (36°F to 46°F). Do not Freeze. Discard unused reconstituted solution after 28 days.” to include the deliverable volume of the reconstituted solution, directions for proper storage of the constituted solution, and an expiration or beyond-use date per USP General Chapters: <7> Labeling in the same visual field. <i>Applicants revision is acceptable</i>
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs Misleading statements</u> 21 CFR 201.6	x			
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15		x		Reduce the prominence of the pink swirl graphic and remove the statement (b) (4) from all panels per 201.15(b)(1). <i>Applicants revision is acceptable</i>
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21CFR 201.100(b)(2)	x			See multiple dose container recommendation
<u>Dispensing container</u> 21 CFR 201.100			x	
<u>Medication Guide</u> 21 CFR 610.60			x	

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	x			
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	x			
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Add "off-white to pale yellow" to include identifying characteristics of the dosage form per 21 CFR 201.57(c)(4) <i>Applicant's revision is acceptable.</i> Add "preservative-free" per 21 CFR 610.61 (e) <i>Applicant's revision is acceptable.</i>
6.2 IMMUNOGENICITY		x		Relocated and revised the language for this standard statement based on our current labeling best practice see draft Guidance for Industry: Labeling for Biosimilar Products) <i>Applicant's revision is acceptable.</i>
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Applicant noted in tracked change version that they [redacted] (b) (4) [redacted] [redacted]. OBP recommended keeping "preservative-free" per 21 CFR 610.61 (e); this paragraph describes the drug product (as lyophilized powder) not as the reconstituted

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				solution. <i>Applicant's accepted our recommendation.</i> Revise the list of inactive ingredients to appear in alphabetical order (see USP Chapter <1091>). <i>Applicant's revision is acceptable.</i> Add the deliverable volume to the sentence: "Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab that delivers xx mL (420 mg trastuzumab-xxxx), at a pH of approximately 6." <i>Applicant's revision is acceptable.</i>
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		Add identifying characteristics, "an off-white to pale yellow", per 21 CFR 201.57(c)(17) <i>Applicant's revision is acceptable.</i>
Manufacturer information For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1		x		Delete " (b) (4) to ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h and includes a placeholder for the US license No. per 21 CFR 610.61(b) Revise as follows: Manufactured by: Mylan GmbH Zurich, Switzerland CH-8050 US License No. xxxx <i>Applicant's revision is acceptable.</i>
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)			x	
Storage and Handling			x	
Ingredients			x	
Manufacturer Information			x	

APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information ([\\cdsesub1\evsprod\bla761074\0040\m1\us\114-labeling\draft-labeling\draft-labeling-text\draft-labeling-text-marked-up-word.doc](#))

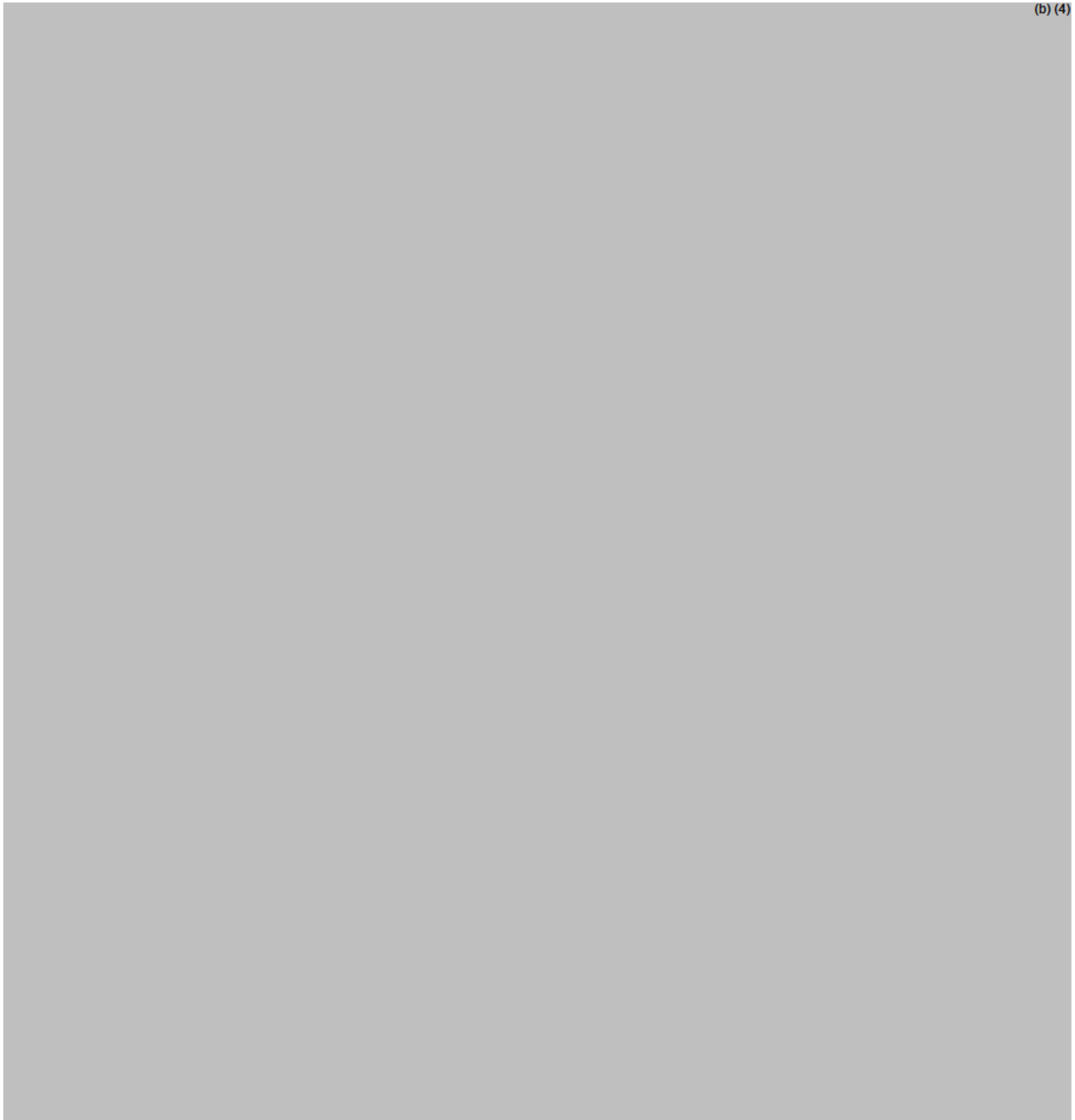
Container Labels submitted July 24, 2017

Mylan's Proposed Draft Vial Label (drug)

(b) (4)

Carton Labeling submitted July 24, 2017

Mylan's Proposed Draft Carton (Front Panel)



(b) (4)

Mylan's Proposed Draft Carton (Top Panel)



Mylan's Proposed Draft Carton (Bottom Panel)



Mylan's Proposed Draft Carton (Side Panel – Left)



Mylan's Proposed Draft Carton (Side Panel – Right)





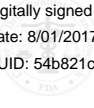
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Kristen
Nickens

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Date: 8/01/2017 10:25:55AM
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Date: May 31, 2017
To: Administrative File, STN 761074/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OPQ/OPF/DMA/BIV
Through: Patricia Hughes, Ph.D., Acting Branch Chief, OPQ/OPF/DMA/BIV
Subject: New Biologic License Application (BLA)
US License: 2062
Applicant: Mylan GmbH.
Facilities: [REDACTED] (b) (4)
Product: MYL-1401O (OGIVRI, a proposed biosimilar to US licensed Trastuzumab)
Dosage: [REDACTED] (b) (4) Vial containing 440 mg MYL-1401O as Lyophilized Powder for Intravenous Infusion to be diluted prior to Intravenous Infusion
Indication: Treatment of patients with HER2 overexpressing breast cancer, metastatic gastric cancer or gastroesophageal junction
Due date: September 03, 2017

Recommendation for Approvability: BLA 761074 is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Mylan GmbH. has submitted BLA 761074 to license MYL-1401O and the associated drug substance and drug product manufacturing processes.

BLA 761074 was submitted in eCTD on November 3, 2016. This review contains the assessment of the manufacturing process of MYL-1401O bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Lakshmi Narasimhan.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
December 16, 2016	Filing requests	0009	January 3, 2017
March 21, 2017	1 to 8	0022	April 4, 2017
	N.A. (specifications)	0024	April 24, 2017
	2d and 6b	0029	May 15, 2017

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

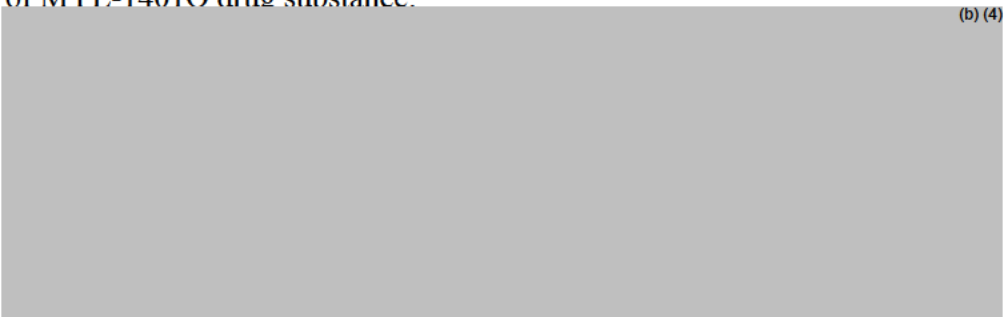
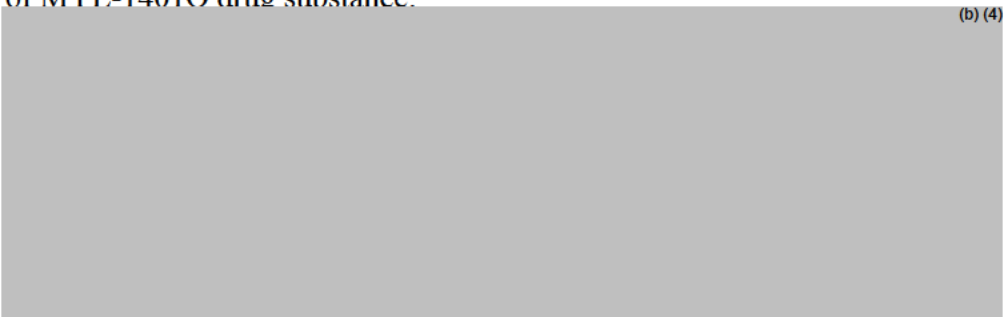
MYL-1401O (a proposed biosimilar to US licensed trastuzumab) is a recombinant humanized monoclonal antibody that specifically binds to the human epidermal growth factor receptor type 2 (HER2).

MYL-1401O is based on the human immunoglobulin G1 kappa; the recombinant antibody is produced in Chinese Hamster Ovary (CHO) cells and has two identical heavy chains and two identical light chains.

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of MYL-1401O drug substance:

-  (b) (4)
- 

Reviewer comments:

A pre-license inspection of  (b) (4) was conducted from  (b) (4). An 8-observation FDA 483 form was issued at the end of the inspection and the initial classification of the facility was VAI. Refer to Panorama for the updated status of the relevant facilities.

S.2.2 Description of the Manufacturing Process and Process Controls

S.2.2.1 Batches and Scale Definition

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S.4.5

(b) (4)

S.6

S.7 Stability

S.7.1 Stability Summary and Conclusions

The proposed shelf-life of MYL-1401O drug substance is (b) (4) months at (b) (4) with the possibility of extension when additional data is available. The stability program includes bioburden and endotoxin tested annually for the long term stability protocol and at 6 months for accelerated conditions at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$., and at 4 weeks for stressed conditions at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

S.7.2 Post-Approval Stability Protocol and Stability Commitment

One commercial batch is added to stability program annually if production occurs during the calendar year. Bioburden and endotoxin samples tested at release, 12, 24, 36, and 48 months will be part of the program.

S.7.3 Stability Data

All bioburden and endotoxin results are compliant with specifications and below the limit of detection, with the exception of one of the accelerated stability batches, which showed 0.06 EU/mg (below AC of (b) (4) EU/mg) at release.

Reviewer Comments:

Microbial quality results of stability samples are not necessarily representative of microbial quality of drug substance stored in different containers. BDS stability is not required from a microbial quality point of view and is deferred to OBP. All bioburden and endotoxin results taken during stability are within specifications.

SATISFACTORY

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

- I. The drug substance part of BLA 761074 was reviewed from a microbial control and microbiology product quality 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 an OBP reviewer.
- III. A pre-license inspection of [REDACTED] (b) (4) was conducted from [REDACTED] (b) (4) [REDACTED]. Refer to Panorama for the updated status of the facility.

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Patricia
Hughes Troost

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