

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761074Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---------------------------------------|--|
| Date of This Review: | August 4, 2017 |
| Requesting Office or Division: | Division of Oncology Products 1 (DOP1) |
| Application Type and Number: | BLA 761074 |
| Product Name and Strength: | Ogivri (trastuzumab-dkst) for Injection, 420 mg/vial |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Rx |
| Applicant/Sponsor Name: | Mylan |
| Submission Date: | January 26, 2017, May 16, 2017, June 28, 2017, and July 24, 2017 |
| OSE RCM #: | 2016-2560 |
| DMEPA Primary Reviewer: | Tingting Gao, PharmD |
| DMEPA Team Leader: | Chi-Ming (Alice) Tu, PharmD |

1 REASON FOR REVIEW

Mylan submitted a 351(k) BLA 761074 for Ogivri (trastuzumab-dkst), a proposed biosimilar to Herceptin (trastuzumab) (BLA 103792).

This review evaluates the submitted Ogivri container labels, carton labeling, and Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors in response to a consult request from Division of Oncology Products 1 (DOP1).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| Human Factors Study | C – N/A |
| ISMP Newsletters | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION

The proposed PI is acceptable from a medication error perspective.

3.2 CONTAINER LABEL AND CARTON LABELING

We evaluated the May 16, 2017 proposed Ogivri container label and the Diluent container label and noted the following:

- Strength statement is presented as “ (b) (4) ” which does not indicate whether this is the total drug amount in the vial.
- The Diluent container label does not indicate that this is a diluent vial.

We evaluated the May 16, 2017 proposed Ogivri carton labeling and noted that although the carton contains 2 vials (drug vial and diluent vial), (b) (4)

We provided the following recommendations to Office of Pharmaceutical Quality (OPQ) Labeling Reviewer to get OPQ concurrence. OPQ communicated our recommendations below in addition to OPQ's labeling comments to Mylan on June 2, 2017.^a

- A. Container label - Ogivri vial
 - 1. Revise the strength statement to "420 mg/vial" for clarity.
- B. Container label - Diluent vial
 - 1. Add a statement to indicate that this is a diluent vial (e.g., "For Drug Diluent Use Only").
- C. Carton labeling
 - 1.  (b) (4)

Mylan submitted revised Ogivri container labels and carton labeling on June 28, 2017 in response to our recommendations above and recommendations from OPQ. We reviewed the June 28, 2017 Ogivri container labels and carton labeling and noted that the nonproprietary name in the preparation instructions and statement of ingredients is presented as "trastuzumab" instead of "trastuzumab-xxxx". Additionally, FDA has designated the nonproprietary name, trastuzumab-dkst, for this product.^b Therefore, we provided the following recommendations to Mylan:

- A. General recommendation
 - 1. Ensure all nonproprietary name on the container label and carton labeling is presented as "trastuzumab-dkst" instead of "trastuzumab".
- B. Container label
 - 1.  (b) (4)
- C. Carton labeling
 - 1. Revise this statement from "The content of each Ogivri™ vial is 420 mg trastuzumab" to "The content of each Ogivri™ vial is 420 mg trastuzumab-dkst".
 - 2. Revise the preparation instructions from "that delivers 20 mL (420 mg trastuzumab)." to "that delivers 20 mL (420 mg trastuzumab-dkst)."

Mylan submitted revised Ogivri container labels and carton labeling on July 24, 2017 and we found the revised Ogivri container labels and carton labeling acceptable from a medication error perspective.

^a The following recommendations were communicated to Mylan on June 2, 2017 in Wheeler, C. "BLA 761074 Carton/Container IR." Message to Barbara Militzer. 2 June 2017. E-mail.

^b Merchant, L. General Advice for BLA 761074. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JULY 18.

4 CONCLUSION

The proposed Ogivri Prescribing Information and the July 24, 2017 revised Ogivri container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ogivri that Mylan submitted on January 26, 2017, and Herceptin retrieved from April 27, 2017 approved Herceptin Prescribing Information^c.

| Table 2. Relevant Product Information for Herceptin and Ogivri | | |
|---|--|-----------------------------------|
| Product Name | Herceptin | Ogivri |
| Initial Approval Date | September 25, 1998 | N/A |
| Active Ingredient | trastuzumab | Trastuzumab-dkst |
| Indication | HER2 overexpressing breast cancer HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma ^d | HER2 overexpressing breast cancer |
| Route of Administration | intravenous | Intravenous |
| Dosage Form | For injection | For injection |
| Strength | 150 mg/vial, 420 mg/vial | 420 mg/vial |
| Dose and Frequency | <p>Adjuvant Treatment of HER2-Overexpressing Breast Cancer</p> <p>Administer at either:</p> <ul style="list-style-type: none"> Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for the first 12 weeks, followed by 6 mg/kg over 30-90 minutes every 3 weeks. Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30-90 minutes IV infusion every three weeks for 52 weeks. <p>Metastatic HER2-Overexpressing Breast Cancer</p> <ul style="list-style-type: none"> Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions. <p>Metastatic HER2-Overexpressing Gastric Cancer^e</p> <p>Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.</p> | |

^c Herceptin. Drugs@FDA. U.S. Food and Drug Administration; April 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103792s5337lbl.pdf.

^d Herceptin's gastric cancer indication is protected by orphan drug exclusivity expiring on October 20, 2017.

^e Herceptin's gastric cancer indication is protected by orphan drug exclusivity expiring on October 20, 2017.

| Table 2. Relevant Product Information for Herceptin and Ogivri | | |
|---|--|---|
| Product Name | Herceptin | Ogivri |
| How Supplied | <p>One carton containing 150 mg Single dose vial</p> <p>One carton containing 420 mg Multi-dose vial and Bacteriostatic Water for Injection</p> | <p>Each carton contains one 420 mg multi-dose vial Ogivri and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.</p> |
| Storage | <p>Store Herceptin vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.</p> | <p>(b) (4) Ogivri (b) (4) at 2° to 8°C (36° to 46°F) (b) (4) reconstitution.</p> |
| Container Closure | <p>Single-dose vial - 15 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap</p> <p>Multi-dose vial - 50 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap</p> | <p>(b) (4) 50 mL glass vial closed with a (b) (4) stopper with (b) (4) (b) (4). The (b) (4) stopper is sealed with an aluminum seal with plastic flip-off cap component.</p> |

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Ogivri labels and labeling submitted by Mylan.

- Container labels submitted May 16, 2017
- Revised container labels submitted June 28, 2017
- Revised container labels submitted July 24, 2017
- Carton labeling submitted May 16, 2017
- Revised carton labeling submitted June 28, 2017
- Revised carton labeling submitted July 24, 2017
- Prescribing Information submitted on January 26, 2017 (Image not shown)

G.2 Label and Labeling Images

Container label – Ogivri vial – submitted May 16, 2017



^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TINGTING N GAO
08/04/2017

CHI-MING TU
08/04/2017

Consult Memorandum

Date: July 26, 2017

To: Charlene Wheeler, MSHS, Sr. Regulatory Project Manager, CDER/OND/OPHOP/DOPI
Jennifer Gao, M.D., Medical Officer, CDER/OND/OHOP/DOPI
Laleh Amiri Kordestani, M.D., Clinical Team Lead, CDER/OND/OHOP/DOPI

From: Eunice Lee, Ph.D., Branch Chief, CDRH/OIR/DMGP/MPCB Eunice Y. Lee -S
2017.07.26 16:30:01 -04'00'

Through: Reena Philip, Ph.D., Director, CDRH/OIR/DMGP
Robert Becker, M.D., Ph.D., Chief Medical Officer, CDRH/OIR
Siyeon Lee, General Attorney, OC/OCC

ICC Number: ICC1700440

Subject: BLA 761074 - revised labeling for OGIVRI and Mylan response

Biomarker(s): HER2

I. BACKGROUND

This memo is a follow up to the CDRH consult memo dated May 24, 2017. At the internal meeting with CDER on June 12, 2017, the agreed upon wording regarding a companion diagnostic for Sections 1.1 and 1.2 of the drug label was as follows:

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

There was discussion that “a trastuzumab product” may be interpreted to extend beyond biosimilars, and it was understood that “a trastuzumab product” refers to a product in which trastuzumab is the primary/active agent, such as a biosimilar.

In the revised label received on July 10, 2017, Mylan removed reference to a companion diagnostic. In response, the sponsor was informed that since a companion diagnostic was considered essential to the safe and effective use of Herceptin, a companion diagnostic is essential to the safe and effective use of Ogivri. The sponsor was requested to provide rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for Ogivri. The sponsor provided a response and reinserted the companion diagnostic wording to the drug label on July 19, 2017.

II. CDRH COMMENT TO CDER

In the sponsor’s response, Mylan concurred that FDA-approved companion diagnostics are important for selecting patients who would benefit from Ogivri. They further noted that given that Ogivri is highly similar to Herceptin based on physico-chemical and biological characterization, nonclinical, pharmacokinetic, safety, efficacy, and immunogenicity data with no clinically meaningful differences with Herceptin, FDA-approved companion diagnostics for Herceptin are expected to serve the same purpose for Ogivri.

We believe Mylan’s response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for Ogivri is adequate. We understand that Ogivri’s

nonproprietary name will include a suffix after the core name of trastuzumab, consistent with the guidance on nonproprietary naming of biological products, which was issued after the companion diagnostics guidance. For purposes of the HER-2 tests approved as companion diagnostics for trastuzumab, CDRH believes that reference to trastuzumab in the device labeling includes not only Herceptin but also products determined to be biosimilar to Herceptin.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUNICE Y LEE
11/29/2017



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: July 10, 2017 **Date Consulted:** June 28, 2017

From: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Oncology Products 1 (DOP1)

Drug: Ogivri (trastuzumab) intravenous infusion

BLA: 761074

Applicant: Mylan GmbH

Subject: Inclusion of Pregnancy Exposure Registry Heading into Subsection 8.1

**Proposed
Indication:**

- The treatment of HER2-overexpressing breast cancer
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

**Materials
Reviewed:**

- DPMH consult request dated June 28, 2017, DARRTS Reference ID 4117358
- PMHS Review for Herceptin (trastuzumab), BLA 103792. Karen Feibus, MD. September 5, 2008.
- DPMH Review of Herceptin (trastuzumab), BLA 103792. Christos Mastroyannis. February 23, 2016. DARRTS Reference ID: 3888024
- Genetech Annual Data Summary of the MoTHER Pregnancy Registry from 1Feb 2016 through 31 January 2017. Submitted April 25, 2017.

INTRODUCTION

On November 2, 2016, Mylan GmbH, submitted a351(k) for Ogivri (trastuzumab), BLA 761074, with the proposed indication of treatment of HER2 overexpressing breast cancer and treatment of HER2-overexpressing metastatic gastric cancer or gastroesophageal junction adenocarcinoma. The biological reference product is Herceptin (BLA 103792), which was originally approved in the U.S on September 25, 1998.

The Division of Oncology Products 1 (DOP1) consulted the division of Pediatric and Maternal Health (DPMH) on June 28, 2017 to determine whether Ogivri labeling should have similar labeling to Herceptin related to a pregnancy exposure registry and pregnancy pharmacovigilance program. DOP1 asked DPMH four specific questions. The questions and responses are provided below.

DOP1 Question #1:

Why were the pregnancy exposure registry and pregnancy pharmacovigilance program established for Herceptin?

***DPMH Response*^{1,2,3}:**

When Herceptin was first approved, it was labeled as a pregnancy category B. On January 18, 2008, Herceptin labeling changed its pregnancy category to a pregnancy category D after there were postmarketing reports of oligohydramnios in nine women who received Herceptin during pregnancy. As a result of the signal, the Agency issued the Sponsor a post marketing commitment (PMC) to establish a pregnancy exposure registry.

In order to better describe adverse pregnancy complications, pregnancy outcomes, fetal/infant outcomes and fetal or infant functional deficits among women with breast cancer treated with Herceptin, Genentech initiated a pregnancy registry, also known as the MotHER (Mother with HER2) registry in December 2008. The MotHER Pregnancy Registry is a U.S.-based, prospective, observational registry of women (≥ 18 years of age) with breast cancer who have been or are being exposed to at least one dose of Herceptin® (trastuzumab) (either alone or as part of a Herceptin-containing regimen), Perjeta (pertuzumab), or Kadcyca (ado-trastuzumab emtansine) during pregnancy or within 7 months prior to conception (regardless of cancer stage at the time of exposure). The MotHER Registry continues to be active and to enroll eligible patients. Cumulative annual interim data summaries for the registry have been provided to the Agency since 2009.

In September 2013, DEPI and PMHS made additional recommendations to the Sponsor regarding the MotHER Registry Protocol. DEPI and PMHS recommended that the Sponsor reinforce the current pregnancy registry with a worldwide enhanced pharmacovigilance program. The Global Enhanced Pharmacovigilance Pregnancy Program was created to

¹ Genentech Annual Data Summary of the MotHER Pregnancy Registry from 1Feb 2016 through 31 January 2017. Submitted April 25, 2017.

² Drugs@FDA. Herceptin. Accessed 6/28/2017.

https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2008/103792s5175ltr.pdf

³ DPMH Review of Herceptin (trastuzumab), BLA 103792. Christos Mastroyannis. February 23, 2016. DARRTS Reference ID: 3888024

collect additional maternal and fetal/infant information from all reports of women exposed to Herceptin, Perjeta and/or Kadcyca during pregnancy, or within seven months prior to conception.

DOP1 Question #2:

When did the information on the pregnancy exposure registry and pregnancy pharmacovigilance program get added to Herceptin's labeling? Was the information added in connection with a PMR? Can you send us the associated letter?

***DPMH Response*^{1,2,4}:**

On January 18, 2008, information about the Cancer and Childbirth Registry was added to Herceptin Labeling. In addition, a post-marketing commitment (PMC) that was issued on January 18, 2008 that stated the following:

To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth / outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

A letter regarding the PMC can be found at [Drugs@FDA](#) under Herceptin.²

The sponsor, Genentech, submitted a protocol summary for the pregnancy registry on June 26, 2008 that was reviewed by the Pediatric and Maternal Health Staff –Maternal Health Team (PMHS-MHT) in a consult review dated September 5, 2008. Genentech initiated the pregnancy registry [a study called MotHER] in December 2008 as a response to the PMC and in agreement with the Agency. Since 2008, two other drugs (pertuzumab and ado-trastuzumab) have been added to the MotHER pregnancy registry.

In September 2013, the Division of Epidemiology (DEPI) and PMHS made additional recommendations to the Sponsor regarding the MotHER Registry Protocol. DEPI and PMHS recommended that the Sponsor reinforce the current pregnancy registry with a worldwide enhanced pharmacovigilance program. Information about the pregnancy pharmacovigilance program was added to Herceptin labeling March 17, 2016.

DOP1 Question #3^{1,2}:

Is the agency still receiving data and evaluating data from Herceptin's pregnancy exposure registry and pregnancy pharmacovigilance program? Do you think the registry and program are still necessary?

⁴ PMHS Review for Herceptin (trastuzumab), BLA 103792. Karen Feibus, MD. September 5, 2008.

DPMH Response:

Yes, the Agency is still receiving data from the Herceptin pregnancy exposure registry; however, given the low number of cases reported to the Herceptin pregnancy registry, DPMH does not think that the Herceptin pregnancy exposure registry is still necessary (see discussion below). However, DPMH recommends that the pregnancy pharmacovigilance program, which could still obtain useful clinical safety information and still be feasible, should be continued.

The latest interim report provided by the Applicant covers the time period from December 20, 2008 (when the registry was initiated) to January 31, 2017. Data have been provided cumulatively and annually. The pregnancy registry is required to enroll patients until December 31, 2019 and continues to be open to enrollment at this time. As of January 31, 2017, a total of 19 patients have been enrolled (17 Herceptin exposed including one Perjeta plus Herceptin exposed, which have been previously reported, and two new Perjeta plus Herceptin exposed patients enrolled since the last annual report one year ago.) The rates of oligohydramnios observed in the pregnancy registry are consistent with those observed in the literature, and no other safety signals or trends have been identified.

DOP1 Question #4:

Should a biosimilar product have similar labeling related to a pregnancy exposure registry and pregnancy pharmacovigilance program?

DPMH Response:

Information about the Herceptin pregnancy exposure registry and pregnancy pharmacovigilance database is specific to Genetech's products (Herceptin, Perjeta, Kadcylla) and cannot be included in Ogivri labeling based on advice and previous discussions with the Therapeutic Biologics and Biosimilars Staff (TBBS), the Office of Regulatory Policy (ORP), and the Office of the Chief Counsel (OCC).

Given the low number of cases reported to the Herceptin pregnancy registry, there is no reason to have Mylan pursue its own pregnancy exposure registry for Ogivri. However, DPMH does recommend that Mylan consider having its own pregnancy pharmacovigilance database for Ogivri.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIRIAM C DINATALE
07/10/2017

LYNNE P YAO
07/10/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 9, 2017

To: **Charlene Wheeler, MSHS**
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **OGIVRI™** (trastuzumab-xxxx) for injection, for intravenous use
BLA 761074

Office of Prescription Drug Promotion comments on proposed
prescribing information (PI), container labels and carton labeling

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI), carton labeling and container labels for OGIVRI™ (trastuzumab-xxxx) for injection, for intravenous use as requested by DOP1 in the consult dated December 1, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "BLA 761074 Draft Label 24May17.doc" sent by electronic mail on May 25, 2017, to OPDP (Kevin Wright) from DOP1 (Charlene Wheeler). OPDP has no comments for the proposed PI.

OPDP also reviewed the proposed container labels and carton labeling submitted to the electronic document on May 16, 2017. OPDP has no comments for the proposed labels and labeling.

If you have any questions, please feel free to contact, Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN WRIGHT
06/09/2017

Clinical Inspection Summary

| | |
|-----------------------------------|---|
| Date | June 2, 2017 |
| From | Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation |
| To | Charlene Wheeler, Regulatory Project Manager Suparna Wedam, Clinical Reviewer Division of Oncology Products 1 |
| BLA # | 761074 |
| Applicant | Mylan GmbH |
| Drug | Hercules (MYL-1401O) |
| NME | Biosimilar |
| Therapeutic Classification | Regular |
| Proposed Indication | MYL-1401O a proposed biosimilar to Herceptin® (trastuzumab, Genentech Inc.) is for the treatment of adjuvant breast cancer, metastatic breast cancer and metastatic gastric cancer. |
| Consultation Request Date | January 18, 2017 |
| Summary Goal Date | June 5, 2017 |
| Action Goal Date | August 18, 2017 |
| PDUFA Date | September 3, 2017 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study MYL-Her 3001 were submitted to the Agency in support of BLA 761074. Three clinical sites, Dr. Alexey Manikhas (Site 1318), Dr. Igor Bondarenko (Site 1006), and Dr. Gia Nemsadze (Site 1402), and a CRO, (b) (4), were selected for audit.

The primary efficacy endpoint, Objective Response (OR) per RECIST 1.1 as determined by an Independent Endpoint Review Committee, was corroborated with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Alexey Manikhas, Dr. Igor Bondarenko, Dr. Gia Nemsadze and CRO (b) (4).

The data from Study MYL-Her 3001 submitted to the Agency in support of BLA 761074, appear reliable based on available information.

II. BACKGROUND

Mylan GmbH (Mylan), as sponsor of BLA 761074, seeks approval to market MYL-1401O Lyophilized Powder for Intravenous Infusion, a proposed biosimilar to Herceptin[®] (trastuzumab, Genentech Inc.). MYL-1401O is proposed to be used for the treatment of adjuvant breast cancer, metastatic breast cancer and metastatic gastric cancer. The application is based, in part, on clinical data that demonstrates that MYL-1401O is highly similar to Herceptin[®] as established by a confirmatory clinical safety and efficacy study (Study MYL-Her 3001).

The following overview of the Study MYL-Her 3001 is intended as background context for interpreting the inspectional findings.

Study MYL-Her 3001 is entitled, “A multicenter, double-blind, randomized, parallel-group, Phase III study of the efficacy and safety of Hercules plus taxane versus Herceptin[®] plus taxane as first line therapy in patients with HER2-positive metastatic breast cancer.” The study was conducted at 95 clinical centers in 17 countries. There were no clinical centers in the United States. A total of 500 subjects were randomized (249 into the MYL-1401O arm and 251 into the Herceptin[®] arm).

Study Period: First subject enrolled: December 10, 2012

Data cutoff date for analysis: January 25, 2016

Primary efficacy endpoint: Independently assessed Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Objectives of Inspections:

- a. Assess objective response as determined by the clinical investigator using RECIST Version 1.1.
- b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- c. General compliance with the investigational plan.

III. RESULTS (by site):

| Name of CI, Site #, Address | Protocol # and # of Subjects | Inspection Date | Final Classification |
|---|---|----------------------|--|
| CI#1: Alexey Manikhas (Site 1318) City Clinical Oncology Center 56, Prospect Veteranov Saint Petersburg 198255 Russia | Protocol: MYL-Her 3001 Subjects: 28 | April 24-28, 2017 | Preliminary Classification VAI |

| Name of CI, Site #, Address | Protocol # and # of Subjects | Inspection Date | Final Classification |
|---|---|----------------------|--|
| CI#2: Igor Bondarenko (Site 1006) Hospital No. 4 31, Blyzhnya Str Dnipropetrovsk State Medical Academy Dnipropetrovsk 49102 Ukraine | Protocol: MYL-Her 3001 Subjects: 27 | April 10-14, 2017 | Preliminary Classification NAI |
| CI#3: Gia Nemsadze (Site 1402) Institute of Clinical Oncology 5 Lubliana str. Tbilisi 0159 Georgia | Protocol: MYL-Her 3001 Subjects: 26 | April 24-28, 2017 | Preliminary Classification NAI |
| CRO: (b) (4) (Location of the Trial Master File) (b) (4) | Protocol: MYL-Her 3001 Site Numbers: 1318, 1006, 1402, 1305 and 1908. | May 8-11, 2017 | Preliminary Classification NAI |

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Alexey Manikhas, M.D. (Site 1318)

The site screened 35 subjects and enrolled 28 subjects. Records of 20 subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms and randomly selected subject source data. The source data was compared to the e-CRF and data listings submitted to the application. Serious Adverse Event (SAE) and all adverse events were also reviewed. No discrepancies were observed.

Source documents at the site corroborated primary efficacy endpoint data reported by the Independent Central Review (IRC) Vendor. There was no evidence of under-reporting of AEs. However, there were several instances in which protocol defined SAEs were not reported to the sponsor within the protocol specified timeframe of 24 hours of the site becoming aware of the SAEs. Subject (b) (6) experienced an SAE of

grade 4 neutropenia on [REDACTED] (b) (6) but was not reported to the sponsor until [REDACTED] (b) (6). Subject [REDACTED] (b) (6) experienced an SAE of grade 4 neutropenia on [REDACTED] (b) (6) but was not reported to the sponsor until [REDACTED] (b) (6). Finally, Subject [REDACTED] (u) (1) experienced an SAE of grade 4 neutropenia on [REDACTED] (b) (6) but was not reported to the sponsor until [REDACTED] (b) (6). Subjects [REDACTED] (b) (6) were enrolled into the test article treatment arm [MYL-1401O + Taxane] and Subject [REDACTED] (b) (6) was enrolled into the active comparator arm [Herceptin + Taxane]. These SAEs are included in the application data sets. These instances of late reporting of an SAE to the sponsor were also included in the protocol deviation data listing for this clinical site. All three subjects fully recovered from the SAEs. While these inspectional observations are protocol violations they should not impact study outcomes or have placed subjects at undue risk.

2. Dr. Igor Bondarenko, M.D. (Site 1006)

The site screened 45 subjects and enrolled 27 subjects. Records of all 27 subjects were reviewed during the inspection. At the time of this inspection ten subjects were in long-term follow up. The inspection included assessment of all informed consent forms and subject source data. The source data was compared to the e-CRF and data listings submitted to the application.

The inspection revealed no significant deficiencies. Source documents at the site corroborated primary efficacy endpoint data reported by the IRC. There was no evidence of under-reporting of AEs.

3. Dr. Gia Nemsadze, M.D. (Site 1402)

The site screened 46 subjects and enrolled 26 subjects. Records of 23 subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, IEC/IRB correspondence and approvals, and financial disclosures and investigator agreements. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. Source documents at the site corroborated primary efficacy endpoint data reported by the IRC. There was no evidence of under-reporting of AEs. Data listings submitted to the application were consistent with source documents. Overall study files were complete and well organized.

4. CRO: [REDACTED] (b) (4) (Location of the Trial Master File)

The inspection of [REDACTED] (b) (4) focused on the control, oversight, and management of Study MYL-Her 3001. Monitoring records were reviewed from five clinical sites (1318, 1006, 1402, 1305 and 1908). Monitoring appeared adequate. There were no noncompliant sites and no sites were closed during the conduct of the study. All clinical investigators and sub-investigators signed financial disclosure

forms and Form FDA 1572s as appropriate. Efficacy data assessed during the inspection is consistent with the primary efficacy endpoint data reported in the application. Standard Operating Procedures were also reviewed with no major deficiencies noted. Reporting practices for AEs, SAEs, and protocol deviations were reviewed for five sites. No deficiencies were noted. There was adequate oversight over the conduct of the study. There was no evidence of under-reporting of AEs/SAEs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. BLA #761074
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/Laleh Amiri-Kordestani
DOP1/Project Manager/Charlene Wheeler
DOP1/Medical Officer/Suparna Wedam
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREN C IACONO-CONNORS
06/02/2017

KASSA AYALEW
06/02/2017

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 2, 2017

TO: Geoff Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Makini K. Cobourne-Duval, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sam Haidar, Ph.D., R.Ph
Deputy Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering BLA 761074 for a clinical
inspection conducted at (b) (4)

Inspection Summary

An inspection of the clinical portion of the study listed in the table below for BLA 761074 (proposed biosimilar to trastuzumab) was conducted at (b) (4) by ORA investigator, Yvonne T. LaCour during March 2017. Based on the information in the EIR, this reviewer recommends accepting the clinical portion of study MYL-HER 1002 (BLA 761074) for further Agency (FDA) review.

Inspected Study

| Application | Medication | Study | Study Site | Sponsor | Recommendation |
|-------------|------------------------------------|--------------|------------|--|----------------|
| BLA 761074 | Proposed biosimilar to trastuzumab | MYL-HER 1002 | (b) (4) | MYLAN GmbH, Thurgauerstrasse 40, CH-8050, Zurich, Switzerland | Acceptable |

Study Number: MYL-HER 1002

Study Title: "A Single-Center, Randomized, Double-Blind, Three-Arm, Parallel-Group Phase I Study to Compare the Pharmacokinetic Profiles of Hercules, EU-Approved Herceptin® and US-Licensed Herceptin® Administered as a Single Intravenous Infusion to Healthy Male Volunteers."

Study Dates:

Clinical Phase: 8/7/2013 (Cohort 1; study initiation) through 2/24/2014 (Cohort 13; study completion)

ORA investigator Yvonne T. LaCour audited the clinical portion of the study listed above for BLA 761074 at [REDACTED] (b) (4) from 03/20/2017 through 03/24/2017. The information the investigator reviewed included records related to dosing, drug accountability, ICFs, adverse events, randomization, and the IRB. At the close of the inspection, no Form FDA-483 was issued at [REDACTED] (b) (4) for BLA 761074. However, one discussion item was discussed with firm's management: a discrepancy in the recorded pre-dose and post-dose intravenous (IV) bag weights for a particular subject when comparing the source document to the eCRF.

Discussion Item

For subject [REDACTED] (b) (6) the pre-dose IV bag weight was recorded in the source document (the preparation worksheet) as 319.38 grams. However in the eCRF, the pre-dose IV bag weight was recorded as 318.98 grams. Additionally, for the same subject, the post-dose IV bag weight was recorded as 56.47 grams in the source document but the same weight was recorded as 63.57 grams (see Attachments 1 and 2).

In response, the firm's management stated that a data processing staffer will check another staffer's data entry into eCRFs from the source document to ensure information is entered accurately and planned to address this item within the next 30 days.

OSIS Assessment

The discussion item appears to be due to an error in the transcription of the recorded weights of the drug product in the IV bag (pre-infusion and post-infusion) from the source document to the eCRF. Given the fact [REDACTED] (b) (6) the appropriate 8 mg/kg dose was administered to subject [REDACTED] (b) (6) based on the preparation worksheet, the transcribing [REDACTED] (b) (6) r for this discussion item does not impact the integrity of the data.

Recommendation

Following an evaluation of the EIR for [REDACTED] (b)(4) and the currently available information, this reviewer concludes that the clinical portion of data from study MYL-HER 1002 (BLA 761074) are reliable and recommends accepting the data for further Agency (FDA) review.

Final Site Classification:

NAI: [REDACTED] (b)(4)
FEI: [REDACTED]

CC:
OSIS/Kassim/Choe/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Choi/Skelly/Au/Cobourne-Duval
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OND/DOPI/Kim

Draft: MCD 06/01/2017, MCD 6/2/2017
Edit: SA 6/1/2017, SA 6/2/2017; SHH 6/2/2017

ECMS:
Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/[REDACTED] (b)(4)
[REDACTED] (b)(4)/BLA 761074 MYL-14010 (proposed biosimilar to trastuzumab)

OSI file #: [REDACTED] (b)(4)
FACTS: [REDACTED]

Attachment 1: Preparation worksheet for subject [REDACTED] (b)(6)
Attachment 2: eCRF information for subject [REDACTED] (b)(6)

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANLEY AU
06/02/2017
Acting Team Lead
Signing on behalf of M. Cobourne-Duval, primary reviewer

SAM H HAIDAR
06/02/2017

Consult Memorandum

Date: May 24, 2017
To: Jennifer Gao, M.D., Medical Officer, CDER/OND/OHOP/DOPI
From: Eunice Lee, Ph.D., Branch Chief, CDRH/OIR/DMGP/MPCB
Through: Reena Philip, Ph.D., Director, CDRH/OIR/DMGP
ICC Number: ICC1700440
Subject: BLA 761074 - draft labeling for OGIVRI
Biomarker(s): HER2

Eunice Y. Lee -S
2017.05.24 18:14:34 -04'00'

I. PURPOSE

A consult request was received from CDER on May 23, 2017, requesting CDRH to comment on the product label for BLA 761074, under sections 1.1, 1.2, and 1.3, regarding the statement for the companion diagnostic. There was no requirement for a companion diagnostic for OGIVRI, since it is a biosimilar to trastuzumab (for which there are FDA-approved companion diagnostic tests). CDER is seeking CDRH input about the following sentence in the sponsor label: "Select patients for therapy based on an FDA-approved companion diagnostic for OGIVRI."

II. CDRH COMMENTS TO CDER

1. Given that there is no companion diagnostic indicated for OGIVRI and the performance of the FDA-approved tests were established in the studies supporting Herceptin approval, we agree that the label should indicate the following: "Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab." Per our email dated May 24, 2017, our edits were added to the draft label on the SharePoint site.
2. Our understanding is that the label for the biosimilar will be nearly the same as that for Herceptin, and therefore, the name of the tests will not be included in the clinical study description (section 14). We agree that the tests should not be named. If, however, the clinical study for OGIVRI will be included with the names of the IHC and FISH tests performed at the central laboratory in the product label, then we would advise that there should be a companion diagnostic specifically indicated for OGIVRI.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUNICE Y LEE
05/25/2017

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 12, 2017

TO: Geoffrey S. Kim, MD
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Hasan A. Irier, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Inspection of (b) (4) covering:
BLA 761074 (MYL-14010, a Proposed Biosimilar to
Trastuzumab, Sponsored by Mylan GmbH)

Summary:

At the request of the Division of the Division of Oncology Products I, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of bioanalytical portions of the following clinical studies conducted by (b) (4) (b) (4). At the closing of inspection, no Form FDA 483 was issued at the site.

During the inspection, we evaluated validations of the methods used in pharmacokinetic, pharmacodynamics, anti-drug antibody (ADA), and neutralizing antibody (NAb) assessments, which were presented as the basis for biosimilarity between MYL-14010 (Hercules) and Herceptin (for both EU-approved and US-licensed Herceptin). At the close of inspection, we discussed several

items (below) with the firm. Although there were no direct regulatory violations or instances of inaccurate reporting in these method validations and studies, these OSIS reviewers recommend that the discussion items and the firm's responses be considered during the application review.

Studies Audited during this Inspection:

I. MYL-Her-1002: "A single-center, randomized, double-blind, three-arm, parallel-group phase I study to compare the pharmacokinetic profiles of Hercules, EU-approved Herceptin® and US-licensed Herceptin® administered as a single intravenous infusion to healthy male volunteers"

(b) (4) analyzed human serum samples collected from subjects participating in study MYL-Her-1002, under the following project designations:

A. Pharmacokinetics (PK) Study #8276627: "Quantitation of Hercules, EU-Approved Herceptin® and US-Licensed Herceptin® in human serum samples from clinical study MYL-Her-1002 using ELISA"

Sample Analysis: 01/7/14 to 05/24/14

B. Anti-Drug Antibody (ADA) Study-#8276624: "Detection of anti-Herceptin (EU and US) and anti-Hercules antibodies in human serum using the MesoScale Discovery (MSD) Platform to support phase I study MYL-Her-1002"

Sample Analysis: 04/10/14 to 05/29/16

II. MYL-HER-3001: "A multicenter, double-blind, randomized, parallel-group, phase III study of the efficacy and safety of Hercules plus taxane versus Herceptin® plus taxane as first line therapy in patients with HER2-positive metastatic breast cancer"

(b) (4) analyzed human serum samples collected from subjects participating in study MYL-Her-3001, under the following project designations:

A. PK Study# 8255211: "Quantitation of Hercules and EU-Herceptin® in human serum samples from clinical study MYL-Her-3001 using ELISA"

Sample Analysis: 01/27/15 to 05/5/16

B. ADA Study# 8255251: "Detection of anti-Herceptin EU and anti-Hercules (Bmab200) antibodies in human metastatic

breast cancer serum using the Mesoscale Discovery (MSD)
platform to support phase III clinical study MYL-Her-3001"

Sample Analysis: 01/13/16 to 03/11/16

C. Neutralizing Antibody (NAb) Study# 8342342: "Analysis for
neutralizing anti-Herceptin EU and anti-Hercules (Bmab200)
antibodies in human metastatic breast cancer serum samples
to support phase III clinical study MYL-Her-3001"

Sample Analysis: 07/14/16 to 07/27/16

D. Her/ECD Study-#8286511: "Quantitation of HER-2/ECD in
human serum samples from clinical study MYL-HER-3001 using
ELISA"

Sample Analysis: 01/24/14 to 07/22/16

OSIS scientists Hasan A. Irier, Ph.D. and Michael F. Skelly,
Ph.D. audited the bioanalytical portions of the above studies
from (b) (4). The audit covered
bioanalytical method validations and serum sample analyses and
immunogenicity studies (ADA and NAb) for the test products in
abovementioned studies. The audit included a thorough review of
facilities and equipment, review of study records and
correspondence, and interviews and discussions with (b) (4)
management and staff.

At the conclusion of the inspection, we did not issue Form FDA
483. However, we discussed the following items:

Discussion Items:

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

(b) (4)

Recommendation:

Following review of the EIR for (b) (4) we
recommend that the Review Division should consider the
Discussion Items listed above prior to accepting data from
studies MYL-Her-1002 and MYL-Her-3001 for review.

Hasan A. Irier, Ph.D.
DGDBE, OSIS

Michael F. Skelly, Ph.D.
DGDBE, OSIS

Final Classification:

NAI: (b) (4)

CC:
OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil/
Mitchell
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au/Irier
Draft: HAI and MFS 4/10/2017; SHH 4/12/17
Edit: MFS 4/11/2017
OSIS file #: (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL
SITES/ (b) (4)
(b) (4) BLA 761074_MYL-14010 (proposed biosimilar to
trastuzumab)

FACTS: (b) (4)

Attachments:

Attachment 1. (b) (4) cover letter and responses to discussion
items

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HASAN A IRIER

04/12/2017

EIR Review for BLA 761074, MYL-1401O [Trastuzumab Powder Concentrate
for Intravenous Infusion (Hercules)] Manufactured by (b) (4) for Mylan GmbH

SAM H HAIDAR

04/13/2017