CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761081Orig1s000

SUMMARY REVIEW
For purposes of this review, the proposed product is referred to by the applicant’s descriptor PF-05280014, which was the name used to refer to this product during development. The proposed proprietary name (Pramuzu) and proposed nonproprietary name (trastuzumab-qyyp) are only conditionally accepted until the application is approved.

Applicant Proposed Indication(s)/Population(s)

**Adjuvant Breast Cancer**

TRAZIMERA is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline-based therapy.

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

**Metastatic Breast Cancer**

TRAZIMERA is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

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

**Metastatic Gastric Cancer**

TRAZIMERA is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.
<table>
<thead>
<tr>
<th>Recommended Indication(s)/Population(s)</th>
<th>Regulatory Action</th>
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  - as part of a treatment regimen with docetaxel and carboplatin  
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| **Metastatic Breast Cancer**           | TRAZIMERA is indicated:  
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  Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product. |
1. Background

On June 22, 2017, the applicant submitted biologics license application (BLA) 761081 under Section 351(k) of the Public Health Service Act for PF-05280014, a proposed biosimilar to US-licensed Herceptin (trastuzumab; henceforth referred to as US-Herceptin). At that time, the applicant was seeking licensure of PF-05280014 for the same indications as US-Herceptin, namely for adjuvant treatment of breast cancer, metastatic breast cancer, and metastatic gastric cancer. During the review of the initial submission for PF-05280014, the Agency concluded that the applicant had adequately demonstrated biosimilarity, but issued a complete response (CR) letter to the applicant on April 20, 2018 on the basis of product quality deficiencies. The review of manufacturing had identified that the methodologies and processes used for Drug Substance (DS) and Drug Product (DP) manufacturing, release testing, and stability testing were not sufficient to assure a consistent and safe product. On September 28, 2018, the applicant submitted responses to address deficiencies identified in the CR letter in their BLA (761081) Class 2 Resubmission. The requested indications are the same as previously requested and the same as the reference product US-Herceptin:

**Adjuvant breast cancer:**
Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer
- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin
- As a single agent following multi-modality anthracycline based therapy
Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Metastatic breast cancer:**
- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease
Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Metastatic gastric cancer:**
- In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

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2 In this document, any reference to “Herceptin” should be considered a reference to US-licensed Herceptin. EU-sourced trastuzumab will be referred to as EU-Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use “trastuzumab”.

Reference ID: 4395827
Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Section 351(i) of the Public Health Service Act (PHS Act) defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product.” Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

In the US, Herceptin is approved as a multi-dose vial containing 420 mg of lyophilized drug product and as a single-dose vial containing 150 mg of lyophilized drug product. In the EU, trastuzumab is marketed only as a single-dose vial containing 150 mg of lyophilized drug product. The applicant developed PF-05280014 as a 420 mg lyophilized powder in a multi-dose vial for reconstitution. The applicant is currently only seeking licensure of the 420 mg presentation.

To support the demonstration that PF-05280014 is highly similar to US-Herceptin, the applicant evaluated and compared PF-05280014 to US-Herceptin using biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The sponsor also performed analytical comparisons of PF-05280014, US-Herceptin and EU-licensed Herceptin (hereinafter EU-Herceptin) to establish the analytical portion of the scientific bridge to justify the use of clinical data generated using EU-Herceptin as the comparator. The applicant also conducted a comparison of the non-clinical PK and toxicity profiles of PF-05280014, US-Herceptin, and EU-Herceptin via intravenous administration in mice. Further, the applicant conducted a PK similarity study, B3271001, and comparative clinical studies (B3271002 and B3271004), to support the demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

The analytical data supported the determination that PF-05280014 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the data submitted from the clinical development program of PF-05280014 supported a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin. Together, the totality of the data thus supported the demonstration of biosimilarity of PF-05280014 to US-Herceptin during the initial review of the dossier. The applicant also provided adequate scientific justification for extrapolation of data to support licensure of PF-05280014 under Section 351(k) as a biosimilar for the conditions of use for which US-Herceptin has been previously approved and for which the applicant sought licensure.
On September 28, 2018, the applicant submitted responses to address deficiencies identified in the CR letter in their BLA (761091) Class 2 Resubmission.

2. **Product Quality**

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<thead>
<tr>
<th>Discipline</th>
<th>Reviewer</th>
<th>Team Leader</th>
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<tbody>
<tr>
<td>Stat-Product Quality (CMC)</td>
<td>Yu-Yi Hsu</td>
<td>Meiyu Shen</td>
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<tr>
<td>OBP</td>
<td>DP/DS</td>
<td>Lymarie Maldonado-Baez</td>
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<td></td>
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<td>Jennifer Swisher</td>
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<td>Rachel Novak</td>
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<td>Microbio Quality</td>
<td>Drug Product</td>
<td>Virginia Carroll</td>
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<td>Drug Substance</td>
<td>Maria Jose Lopez-Barragan</td>
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<td>(Pepe)</td>
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<td>OBP-Labeling</td>
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<td>Facilities</td>
<td>Zhong Li</td>
<td>Peter Qiu</td>
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<td>RBPM</td>
<td>Anh-Thy Ly</td>
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The product quality deficiencies described in the CR letter dated April 20, 2018 have been addressed in the resubmission. Overall, the OPQ review of product quality in the resubmission and in the initial BLA submission have confirmed that the processes and methods used for drug substance and drug product manufacturing, release, and stability testing are sufficient to assure a consistent and safe product.

The commercial manufacture of PF-05280014 drug substance (DS) and drug product (DP) at Pfizer Manufacturing Belgium NV, Belgium (FEI 1000654629), respectively, is recommended for approval by the Division of Inspectional Assessment (DIA, OPF, OPQ). A facility review (dated January 19, 2018) from the original BLA submission concluded that all proposed manufacturing and testing facilities were acceptable based on CGMP compliance status and relevant inspectional coverage. In this resubmission, there were no changes with regards to the GMP facility-related information and is recommended for approval from a facilities assessment perspective.

Key changes made by the applicant during this review cycle are included in the CMC executive summary dated January 11, 2019.

3. **Nonclinical Pharmacology/Toxicology**

Refer to the CDTL review filed in DARRTS on April 20, 2018.
4. **Clinical Pharmacology**  
Refer to the CDTL review filed in DARRTS on April 20, 2018.

5. **Clinical Microbiology**  
Refer to the CDTL review filed in DARRTS on April 20, 2018.

6. **Clinical/Statistical- Efficacy**  
Refer to the CDTL review filed in DARRTS on April 20, 2018.

7. **Safety**  
Refer to the CDTL review filed in DARRTS on April 20, 2018 and the clinical review dated February 26, 2019. The resubmission included additional 18 month follow up of patients enrolled on the comparative clinical study with the original BLA submission, with no new patients enrolled or randomized. No new safety signals were identified.

8. **Advisory Committee Meeting**  
An advisory committee meeting was not held for this application.

9. **Pediatrics**  
Refer to the CDTL review filed in DARRTS on April 20, 2018.

10. **Other Relevant Regulatory Issues**  
Refer to the CDTL review filed in DARRTS on April 20, 2018.

11. **Labeling**  
*Prescribing Information*  
The draft labeling submitted by the applicant to BLA 761081 on February 5, 2019 is adequate from a review perspective.

12. **Recommendations**  
*Recommended Regulatory Action*  
All deficiencies included in the April 20, 2018 CR letter have been adequately addressed by the applicant. In considering the totality of the evidence, the data submitted by the applicant show that PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically
meaningful differences between PF-05280014 and US-Herceptin in terms of safety, purity and potency; therefore, we recommend approval of BLA 761081 for PF-05280014 as a biosimilar to US-Herceptin for the following indications for which US-Herceptin is currently licensed and for which Pfizer is seeking licensure:

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TRAZIMERA is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
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Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Risk Evaluation and Management Strategies (REMS)
A REMS is not indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
Post-Marketing Commitments:

- Develop and implement a peptide mapping method for release and stability testing of PF-05280014 drug substance and drug product that can adequately assess levels of isomerized Asp102. Submit the final validation report and the release and stability acceptance criteria as a Prior Approval Supplement.
- Re-evaluate PF-05280014 drug substance lot release and stability specifications for potency by the FcyRIIIa reporter gene assay and for the CEX-HPLC assay to quantify acidic, main, and basic species after 30 additional drug substance lots have been manufactured at the commercial scale. Submit the corresponding data, analysis, and
statistical plans used to evaluate the specifications, and any proposed changes to the specifications as a Prior Approval Supplement.

- Re-evaluate PF-05280014 drug product lot release and stability specifications for potency by the FcyRIIIa reporter gene assay and for the CEX-HPLC assay to quantify acidic, main, and basic species after 30 additional drug product lots have been manufactured at the commercial scale. Submit the corresponding data, analysis, and statistical plans used to evaluate the specifications, and any proposed changes to the specifications as a Prior Approval Supplement.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J GAO
02/26/2019 10:10:44 AM

LALEH AMIRI KORDESTANI
02/26/2019 10:12:44 AM
## Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>Electronic Stamp Date</th>
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<tbody>
<tr>
<td>From</td>
<td>Laleh Amiri-Kordestani, M.D. (CDTL and Acting Associate Director)</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td>NDA/BLA #</td>
<td>351(k) BLA 761081</td>
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<tr>
<td>Applicant</td>
<td>Pfizer</td>
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<td>Date of Submission</td>
<td>June 22, 2017</td>
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<td>April 22, 2018</td>
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<td>Proprietary Name / Established (USAN) names</td>
<td>TRAZIMERA/Trastuzumab-qqyp PF-05280014 Lyophilized Powder for Intravenous Infusion</td>
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<td>Dosage forms / Strength</td>
<td>lyophilized powder for injection/420 mg per vial</td>
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<td>Proposed Indication(s)</td>
<td>TRAZIMERA is a HER2/neu receptor antagonist indicated for:</td>
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<tr>
<td></td>
<td>1. Adjuvant breast cancer:</td>
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<tr>
<td>Recommended:</td>
<td>Complete Response</td>
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<tr>
<td>Recommended Indication (if applicable)</td>
<td>Not applicable</td>
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# REVIEW TEAM

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Reviewer</th>
<th>TL</th>
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</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Sara Horton</td>
<td>Laleh Amiri-Kordestani (CDTL)</td>
</tr>
<tr>
<td>Non-clinical</td>
<td>Claudia Miller</td>
<td>Tiffany Ricks</td>
</tr>
<tr>
<td>Statistical</td>
<td>Hui Zhang</td>
<td>Shenghui Tang and Jason Schroeder</td>
</tr>
<tr>
<td>Stat-Product Quality (CMC)</td>
<td>Yu-Yi Hsu (1&lt;sup&gt;o&lt;/sup&gt;)</td>
<td>Yi Tsong</td>
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<td></td>
<td>Meiyu Shen (2&lt;sup&gt;o&lt;/sup&gt;)</td>
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<td>Clin-pharmacology</td>
<td>Christy John</td>
<td>Sarah Schrieber</td>
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<td>ORP</td>
<td>Patrick Raulerson</td>
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<td>OBP Substance Quality</td>
<td>Kevin (Cishan) Li</td>
<td>Rachel Novak (ATL)</td>
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<tr>
<td>TBBS</td>
<td>Michele Dougherty</td>
<td>Leah Christl</td>
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<tr>
<td>OSE-RPM</td>
<td>Frances Fahnbulleh</td>
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<tr>
<td>OSE/DMEPA</td>
<td>Tingting Gao</td>
<td>Alice Chi-Ming Tu</td>
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<tr>
<td></td>
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<td>Danielle Harris (Acting DD)</td>
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<tr>
<td>OSI Consult</td>
<td>Lauren Iacono-Connor</td>
<td>Susan Thompson</td>
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<td>OPDP</td>
<td>Kevin Wright</td>
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<td>CDRH Consult</td>
<td>Jacob Richards</td>
<td>Eunice Lee</td>
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<td>PeRC RHPM</td>
<td>Gettie Audain</td>
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<td>OSIS Consult</td>
<td>Mohsen Rajabi Abhari</td>
<td>Gopa Biswas</td>
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<td></td>
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<td>Arindam Dasgupta (DD)</td>
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<td>Kara Scheibner</td>
<td>Michael Skelly</td>
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<td>John Kadavil (DD)</td>
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1. Introduction

On June 22, 2017, the applicant submitted a biologics license application (BLA) under the 351(k) pathway of the Public Health Service Act (PHS Act) for PF-05280014, a proposed biosimilar to US-licensed Herceptin (trastuzumab), hereinafter US-Herceptin\(^1\). The applicant is seeking licensure of PF-05280014 for the same indications as US-Herceptin:

Adjuvant breast cancer:
   a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
   b. With docetaxel and carboplatin
   c. As a single agent following multi-modality anthracycline based therapy

Metastatic breast cancer (MBC):
   a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
   b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Metastatic gastric cancer:
   a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product.” Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

To support the demonstration that PF-05280014 is highly similar to US- Herceptin, the applicant evaluated and compared PF-05280014 to US- Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The sponsor also performed analytical comparisons of PF-05280014, US-Herceptin and EU-licensed Herceptin (hereinafter EU-Herceptin) to establish the analytical portion of the scientific bridge to justify the use of clinical data generated using EU-Herceptin as the comparator.

\(^1\) In this document, any reference to “Herceptin” should be considered a specific reference to US-licensed Herceptin. EU-sourced trastuzumab will be referred to as EU-Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use “trastuzumab”.

Reference ID: 4251658
The applicant also conducted a comparison of the non-clinical PK and toxicity profiles of PF-05280014, US-Herceptin, and EU-Herceptin via intravenous administration in mice.

Further, the applicant conducted a PK similarity study, B3271001, and comparative clinical studies (B3271002 and B3271004), to support the demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

The analytical data submitted supports the conclusion that PF-05280014 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. The amino acid sequences of PF-05280014 and US-Herceptin are identical and a comparison of the secondary and tertiary structures and the impurity profiles of PF-05280014 and US-Herceptin support the conclusion that the two products are highly similar. Inhibition of proliferation of HER2 expressing cells and ADCC activity, which reflect the presumed primary mechanisms of action of US-Herceptin, were determined to be equivalent. HER2 binding is similar between PF-05280014 and US-Herceptin. Some tests indicate that small differences in low abundance glycan forms exist and are likely an intrinsic property of PF-05280014 due to the manufacturing process. High mannose and sialic acid containing glycans can impact PK; however, the differences in total mannose forms and sialic acid were addressed by the ADCC similarity and by the PK similarity between PF-05280014 and US-Herceptin. Subtle differences in charge related variants were detected; however, these differences are not expected to impact the biological activity of PF-05280014. In conclusion, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. The data also support that the analytical portion of the scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014 was established, providing support for the use of clinical data generated with EU-Herceptin to support a demonstration of biosimilarity of PF-05280014 to US-Herceptin. Data provided also support the conclusion that PF-05280014 meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

However, there were several issues with the Drug Substance (DS) and Drug Product (DP) control strategy. The review of manufacturing has identified that the methodologies and processes used for DS and DP manufacturing, release testing, and stability testing are not sufficient to assure a consistent and safe product.

The pharmacokinetics and toxicity profile of PF-05280014 was compared head-to-head with EU-Herceptin and US-Herceptin via intravenous administration in mice. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with PF-05280014 or differences in the PK or toxicity profile of PF-05280014 compared to US-Herceptin in mice.

The pharmacokinetic similarities of PF-05280014, EU-Herceptin and US-Herceptin were evaluated in Study B3271001. The results of this human pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin. The results of this study also established the pharmacokinetic component of the scientific bridge between EU-Herceptin, PF-05280014, and US-Herceptin. Through analytical...
and pharmacokinetic data, the applicant established an adequate scientific bridge between EU-Herceptin, PF-05280014, and US-Herceptin to justify the relevance of clinical data generated using EU-Herceptin to support a demonstration of biosimilarity of PF-05280014 to US-Herceptin.

The results of the clinical development program indicate that the applicant’s data support a determination of no clinically meaningful differences between PF-05280014 and US-Herceptin in terms of safety and efficacy in the indication studied (metastatic breast cancer). Specifically, in the comparative clinical study, Study B3271002, the primary endpoint of overall response rate (ORR) ratio between the two treatment groups, as assessed by central radiology review, was 0.940 (95% CI: 0.842, 1.049) (PF-05280014 over EU-Herceptin), which was within the prespecified 0.80 to 1.25 equivalence margin. Anti-drug antibodies were measured in study B3721002 comparing PF-05280014 to EU-Herceptin. The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products.

An additional PK and clinical study, Study 1004 (B3271004), was conducted comparing PF-5280014 in combination with Taxotere and carboplatin versus EU-Herceptin in combination with Taxotere and carboplatin in patients with operable HER2-positive breast cancer in the neoadjuvant setting. The primary endpoint was the percentage of patients reporting trough plasma concentration (Ctrough) >20 µg/mL at Cycle 5 (Cycle 6 pre-dose), and a secondary efficacy endpoint of pathological complete response (pCR) and ORR. The pathological complete response (pCR) was comparable in both treatment arms (PF-05280014: 46.5% versus EU-Herceptin 48.3%), as was the ORR (PF-05280014: 88.1% versus EU-Herceptin 82.0%) in the per-protocol (PP) population. The safety findings of studies B3271002 and B3271004 were reviewed, and overall no meaningful differences were found in the safety populations.

The applicant is seeking indications that are the same as those for US-Herceptin and provided adequate scientific justification for extrapolation of data and information to support licensure of PF-05280014 as a biosimilar for the condition of use for which US-Herceptin has been previously approved.

In considering the totality of the evidence, the data submitted by the applicant show that PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and supports a demonstration that there are no clinically meaningful differences between PF-05280014 and US-Herceptin in terms of safety, purity, and potency; however, due to manufacturing and control deficiencies, described in further detail in section 3 of this review, the application is not recommended for approval.

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety, purity, and potency of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement
of product specific nonclinical and clinical data.

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product in each indication based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both standalone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

The ‘totality of the evidence’ submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes comparative structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed biosimilar product with the US-licensed reference product. When an applicant’s proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

**Regulatory History**

**February 10, 2012**: Biologics Product Development, Pre-IND Meeting
Discussed FDA’s position that, to support the 3-way scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014, the 3 arm PK similarity study (B3271001) should include a direct comparison of PK between US-Herceptin and PF-05280014. Extrapolation would be possible with sufficient scientific justification.

**July 12, 2013**: Biologics Product Development, Type 3 Meeting
Discussed FDA’s agreement with the phase 3 study primary endpoint of ORR by week 25. FDA advised Pfizer to recalculate sample size using the risk ratio instead of an absolute
difference in response rate. FDA requested an additional study to further evaluate pyrexia finding in the phase 1 PK study. FDA agreed that the phase 3 study could proceed.

**June 22, 2017:** BLA 761081 submitted to FDA.

### 3. CMC/Device

*Source: CMC/Quality/Micro/Facilities Review Team*

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**Final Product Quality Team Recommendation:** Complete Response

**General Product Quality Considerations**

Trastuzumab is an IgG1 monoclonal antibody (mAb) that binds to HER2 antigen and subsequently inhibits HER2 receptor dimerization and downstream signaling, increases destruction of the endocytic portion of the HER2 receptor and inhibits HER2 extracellular domain shedding. The binding of the antibody to effector cells also mediates antibody dependent cellular cytotoxicity (ADCC).

The PF-05280014 drug substance is a humanized IgG1κ monoclonal antibody produced in genetically engineered CHO cells. PF-05280014 drug product (DP) is manufactured to the same strength and presentation as US- Herceptin at 420 mg/vial; however, PF-05280014 has a different formulation of histidine, sucrose, polysorbate 20, pH 6.0. PF-05280014 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.
For the analytical similarity assessment, PF-05280014 was evaluated and compared to US-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The amino acid sequences of PF-05280014 and US-Herceptin are identical, and a comparison of the secondary and tertiary structures and the impurity profiles of PF-05280014 and US-Herceptin support the conclusion that the two products are highly similar.

Inhibition of proliferation of HER2 expressing cells and ADCC activity, which reflect the presumed primary mechanisms of action of US-Herceptin, were determined to be equivalent. HER2 binding is similar between PF-05280014 and US-Herceptin. The data submitted by the applicant support the conclusion that PF-05280014 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, PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.

However, the manufacturing review has identified that the methodologies and processes used for drug substance and drug product manufacturing, release testing, and stability testing as submitted in the initial BLA submission are not sufficient to assure a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents.

Please refer to the complete response letter for the list of deficiencies.

**Microbiology Reviews**

Dr. Maria Jose Lopez-Barragan (DS microbiology review) recommended approval of the BLA from a microbial control and microbiology product quality perspective.

Virginia Carroll (DP microbiology review) recommended a Complete Response of the BLA from a sterility assurance and microbiology product quality perspective. Please refer to Dr. Carroll’s review for additional discussion of the deficiencies.

Please refer to the complete response letter for the list of deficiencies.

**Facilities Review/Inspection**

A pre-license inspection (PLI) of the Drug Substance manufacturing site was conducted from October 2nd through October 6th, 2017 and was found satisfactory. The pre-license inspection for the drug products manufacturing site was waived.
Analytical Similarity Assessment
The analytical similarity assessment was performed to demonstrate that PF-05280114 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components. The similarity assessment also established the analytical portion of the scientific bridge among PF-05280114, US-Herceptin, and EU-Herceptin to justify the relevance of the comparative clinical data generated using EU-Herceptin.

For analytical similarity, PF-05280114 was evaluated and compared to US-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action.

PF-05280114 was found to have the same primary, secondary, and tertiary structure as US-Herceptin and EU-Herceptin. Analysis by CEX-HPLC showed similar number of peaks, retention times, and % acidic species among PF-05280114, US-Herceptin, and EU-Herceptin. Differences were noted in the charge profile by CEX-HPLC when comparing PF-05280114 to US-Herceptin and EU-Herceptin. PF-05280114 had increased levels of basic species, with concomitant decrease in the neutral peak, compared to those of US-Herceptin and EU-Herceptin. Both attributes fell slightly outside the quality range (QR) established based on data from US-Herceptin and EU-Herceptin. Further analysis by digesting the products with carboxypeptidase demonstrated a similar charge profile and indicates that the increase in basic species was due to increase C-terminal lysine present on PF-05280114. C-terminal lysine has been shown to be cleaved upon administration at physiological pH. No impact on potency determined using bioassays was observed. Therefore, this difference does not preclude a demonstration of highly similar between PF-05280114 and US-Herceptin or establishment of the analytic component of the three-way scientific bridge.

Levels of sialylation and galactosylation were similar among all three products. PF-05280114 lots had slightly less afucosylated and high mannose species compared to those of US-Herceptin and EU-Herceptin; however, the results for PF-05280114 lots were within the quality range for these glycan species. Therefore, these differences do not preclude a demonstration of highly similar between PF-05280114 and US-Herceptin or establishment of the analytical component of the three-way scientific bridge.

No differences were observed in biological activity between PF-05280114 and US-Herceptin using any of the biological assays. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, PF-05280114 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. In addition, the analytical component of the three-way scientific bridge has been adequately established. Also, PF-05280014 meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Reviewer Comment: I concur with CMC/OBP review team’s conclusion that data support a demonstration that PF-05280014 is highly similar to US-Herceptin. The data also establish the analytical component of the three-way scientific bridge.
**CDRH**

A CDRH consult was obtained 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. Per CDRH reviewers (Drs. Jacob Richards, Eunice Lee, and Reena Philip), CDRH agreed with the CDER review team that the label should indicate the following: “Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.”

The applicant was requested to provide a rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for PF-05280014. The applicant provided a response on January 24, 2018. CDRH reviewers concluded that applicant’s response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for PF-05280014 is adequate. Moreover, 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. Based on the applicant’s justification and the proposed therapeutic labeling in section 14 referencing the original trastuzumab clinical studies, CDRH agreed that the language regarding “an FDA-approved companion diagnostic for a trastuzumab product” would be acceptable for the PF-05280014 label.

4. Nonclinical Pharmacology/Toxicology

*Source: Pharmacology and Toxicology Review (Drs. Claudia P Miller and Tiffany Ricks)*

**Final Pharmacology/Toxicology Team Recommendations:** Approval.

Two nonclinical animal studies were submitted in support of this BLA: (1) a single-dose comparative toxicokinetic study, including evaluation for anti-drug antibodies (ADA), with PF-05280014, US- Herceptin and EU- Herceptin in male CD-1 mice and (2) a noncomparative, 2-week, repeat-dose toxicity study in male and female CD-1 mice with PF-05280014.

Overall, based on the nonclinical studies provided in this BLA submission, there was no evidence to indicate potential clinical safety concerns associated with PF-05280014 administration. Overall results from the single-dose comparative study demonstrated that tolerability, toxicokinetic profile and ADA responses to PF-05280014 were comparable to US-Herceptin and EU- Herceptin. These results did not identify differences in the PK or toxicity profile (mortality, clinical signs and body weight) among PF-05280014 and US-licensed Herceptin and EU-approved Herceptin. In the repeat-dose study, administration of PF-005280014 to mice did not reveal any toxicity findings compared to vehicle-treated mice.

**Reviewer Comment:** I concur with nonclinical team’s conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of PF-05280014 and US-licensed Herceptin in mice.
5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Christy S. John, Sarah J. Schrieber and Nam Atiqur Rahman)

Final Clinical Pharmacology Team Recommendations: Approval

The objectives of the clinical pharmacology program were to evaluate the pharmacokinetic (PK) similarity between PF-05280014 and US-Herceptin and to support the scientific bridge between PF-05280014, US-Herceptin and EU-Herceptin. The Applicant submitted Study B3271001 which evaluated the PK similarities of PF-05280014, EU-Herceptin and US-Herceptin.

Evidence of PK similarity was demonstrated between PF-05280014 and US Herceptin, as well as the PK portion of the scientific bridge between PF-05280014, US- Herceptin, and EU-Herceptin. The 90% CI of the geometric mean ratio for each product pairwise comparison for the primary pre-specified PK endpoint of AUC\(_{0-\text{inf}}\) fell within the pre-specified margin of 80 to 125%. Study B3271001 was a single-dose, randomized, double-blind, 3-arm, parallel group study in 105 healthy male subjects designed to determine the PK similarity of PF-05280014, US-Herceptin and EU-Herceptin following a single 6 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of PK endpoint AUC\(_{0-\text{inf}}\) were within the pre-specified limits of 80 – 125%. The results of the study established the PK similarity between PF-05280014 and US-Herceptin and provide the PK element of the scientific bridge to justify the relevance of the comparative data generated using EU-Herceptin in Study 3271002 and 3271004 to support a demonstration of biosimilarity to US-Herceptin.

Immunogenicity

The incidence of immunogenicity for PF-05280014 and EU-Herceptin was compared in a multiple-dose, parallel-arm study in 707 patients with breast cancer (B3721002). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or PK endpoints was observed. In conclusion, the data indicate that there is no increase in immunogenicity risk for PF-05280014 as compared to EU-Herceptin, which supports the demonstration that there are no clinically meaningful differences between PF-05280014 and US-licensed Herceptin.

Reviewer Comment: I concur with clinical pharmacology team’s conclusion that the submitted clinical pharmacology study adequately demonstrated similarity of PK among PF-05280014, US-Herceptin and EU-Herceptin. The evidence of PK similarity supports a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin. Also, the PK similarity data establish the PK component of the scientific bridge to justify the relevance of the comparative clinical data generated using EU-Herceptin to
support a demonstration of the biosimilarity of PF-05280014 to US-Herceptin. The immunogenicity data indicate that there is no increase in immunogenicity risk for PF-05280014 when compared to EU-Herceptin, which supports a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Sara Horton, and Hui Zhang and Shenghui Tang)

Final Clinical/Statistical Team Recommendations: Approval

The applicant submitted comparative clinical studies B3271002 and B3271004 to support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

Study B3271002 Schema

Study treatment: Trastuzumab 4 mg/kg IV, then weekly 2 mg/kg; Week 33 changed to 6 mg/kg Q3 weekly Paclitaxel 80 mg/m² Days 1, 8, and 15 (during 28-day cycle), 6 cycles

Study 1002 was a multicenter, double-blind, randomized comparative study evaluating the efficacy, safety, PK, and immunogenicity of PF-05280014 in combination with paclitaxel versus EU-Herceptin with paclitaxel in patients with HER2-positive metastatic breast cancer in the first-line treatment setting. Patients were randomized 1:1 to either PF-05280014 plus paclitaxel or EU-Herceptin plus paclitaxel. Randomization was stratified by prior trastuzumab exposure (yes versus no) and estrogen receptor (ER) status (ER positive versus ER negative).

Primary Endpoint
Objective Response Rate (ORR), evaluating responses achieved by Week 25 and subsequently confirmed, based on the assessments of the central radiology review in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Endpoints
- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions, and laboratory abnormalities;
- Duration of response (DOR), 1-year progression-free survival (PFS) rate and 1-year survival rate;
- Peak and trough PF-05280014 and EU-Herceptin concentrations at selected cycles;
- Incidence of anti-drug (trastuzumab) antibodies (ADA), including neutralizing antibodies (Nab).

Sample size Calculations
To provide approximately 85% power to demonstrate equivalence between PF-05280014 and EU-Herceptin on the primary ORR analysis (ratio of ORR) with the pre-defined equivalence margin of (0.80, 1.25), a sample size of 630 patients (315 per treatment arm) was required. Accounting for a possible 10% attrition rate, the sample size was increased to 690. This sample size calculation assumed that the ORR would be approximately 60% in both treatment arms and the ORR ratio of PF-05280014 to EU-Herceptin was to be analyzed with a two-sided 95% confidence interval (CI). If the 95% CI completely fell in the equivalence region defined as 0.80-1.25, the equivalence would be declared. The equivalence region was derived using a random-effect meta-analysis of historical trastuzumab trials to estimate the treatment effect of trastuzumab with taxane versus taxane alone.

Results
This was an international study with patients enrolled from 24 countries in the ITT population. The ratio of ORR between the two treatment arms was 0.94 with a 95% CI of (0.84, 1.05) and a 90% CI of (0.86, 1.03), both of which were within the pre-defined equivalence margins of 0.80 and 1.25. The difference in ORR between the two arms was -4.0% (95% CI: -11.0%, 3.1%; 90% CI: -9.9%, 1.9%). ORR per central review was also evaluated in the PP population. The ORR was 71.1% in the PF-05280014 arm and 74.4% in the EU-Herceptin arm. The ratio of ORR is 0.96 (95% CI: 0.86, 1.06; 90% CI: 0.88, 1.04). The ratio was within the pre-defined equivalence margins. Results from the PP population are consistent with those from the ITT population. Results of ORR sensitivity analyses per central review or investigator assessment in different analysis populations are consistent with the primary findings. PFS HR was close to 1. There was no apparent difference in PFS between the two arms. The OS results are immature. The median time to death could not be estimated in either treatment arm due to the small number of deaths observed. OS HR was close to 1. There was no apparent difference in OS between the two arms.
Supportive Study – Study B3271004: This study is a noninferiority, double-blind, randomized study evaluating the PK, efficacy, safety, and immunogenicity of PF-05280014 in combination with docetaxel and carboplatin versus EU-Herceptin in combination with docetaxel and carboplatin in patients with operable HER2-positive breast cancer in the neoadjuvant setting. Patients were randomized 1:1 to either PF-05280014 plus docetaxel and carboplatin or EU-Herceptin plus docetaxel and carboplatin. Randomization was stratified by primary tumor size (<5 cm, or ≥5 cm), ER status (ER positive versus ER negative) and by progesterone receptor status (progesterone receptor positive versus progesterone receptor negative).

Primary Objective of the study was to compare the percentage of patients with steady state (Cycle 5) Ctrough >20 µg/mL between PF-05280014 versus EU-Herceptin in patients with operable HER2-positive breast cancer who receive therapy together with Taxotere and carboplatin in the neoadjuvant setting.

Pathologic complete response (pCR) was a secondary endpoint in Study 1004. The analysis of pCR was conducted in the per-protocol population. Forty-seven patients (46.5%) out of 101 patients in the PF-05280014 arm and 43 patients (48.3%) out of 89 patients in the EU-Herceptin arm had a pCR. The pCR rates were comparable between the two treatment arms that further supports that there are no clinically meaningful differences between PF-05280014 and US-Herceptin.

**Reviewer Comment:** I concur with clinical and statistical team’s conclusion that the submitted clinical data demonstrated no differences in terms of efficacy between PF-05280014 and EU-Herceptin. As the Applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for PF-05280014, EU-Herceptin and US-Herceptin (please see sections 3 and 5), the efficacy results of Study 1002 and 1004 support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

**8. Safety**

*Source: Combined Clinical/Stat Review (Dr Sara Horton and Dr Hui Zhang)*

The safety population in the randomized comparative clinical study B3271002 consisted of all patients (n=702) who received at least one dose of study drug. The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. Major events of interest are those listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity.

In addition, the applicant combined patient data from Studies B3271002 and B3271004 for pooled analysis. Overall, the pooled safety population included 462 patients in the PF-05280014 group and 465 patients in the EU-Herceptin group. The incidence of TEAEs, AEs of CTCAE Grade 3 or higher, and SAEs were comparable across treatment groups, and there
were no notable discrepancies between the pooled PF-05280014 group and the pooled EU-Herceptin group.

**Reviewer Comment:** The comparative safety results obtained from Study B3271002, which compared PF-05280014 and EU-Herceptin in HER2 positive metastatic breast cancer patients, and in B3271004, which compared PF-05280014 and EU-Herceptin in the neoadjuvant setting, did not show any meaningful differences in safety between arms. I concur with clinical reviewer’s conclusion that the submitted clinical data adequately supports a finding that there are no clinically meaningful differences in terms of safety between PF-05280014 and US-Herceptin.

9. Considerations for Extrapolation of Biosimilarity

*Source: Combined Clinical/Stat Review (Drs. Sara Horton and Hui Zhang)*

The applicant seeks licensure for all indications for which US-Herceptin is licensed. However, the PF-05280014 clinical program provides clinical efficacy and safety data largely from a clinical program in patients with metastatic BC.

The applicant has submitted the following scientific justifications for extrapolation of data and information submitted in the application to support licensure as a biosimilar for the conditions of use for which US-licensed Herceptin has been previously approved:

- “PF-05280014 is structurally and functionally similar to Herceptin and shares the same mechanism of action (MoA) across all indications.”
- “The data supports a similar PK profile between PF-05280014 and Herceptin.”
- “The biodistribution/disposition mechanisms for PF-05280014 are expected to be similar to those of Herceptin.”
- “PF-05280014 has demonstrated similar clinical efficacy to Herceptin in MBC, with no clinically meaningful differences in safety and immunogenicity. Efficacy in MBC, adjuvant breast cancer and metastatic gastric cancer is related to the shared MoA. The statutory requirements for biosimilarity have been met, and PF-05280014 is expected to have a similar efficacy, safety, and immunogenicity profile as Herceptin in MBC.”

As described in the Guidance for Industry: “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009”, if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for...
which the reference product is licensed. The Applicant has demonstrated that PF-05280014 is highly similar to US-Herceptin based on extensive analytical data and that there are no clinically meaningful differences in safety and efficacy between PF-05280014 and US-Herceptin which supports extrapolating the data to other indications (adjuvant breast cancer and metastatic gastric cancer). The reviewers consider extrapolation to be scientifically justified.

**Reviewer Comment:** I concur with clinical team’s conclusion that the evidence indicates that the extrapolation of data, including clinical data, to support licensure as a biosimilar for the conditions of use for which US-licensed Herceptin has been previously approved is scientifically justified.

10. **Advisory Committee Meeting**

An advisory committee meeting was not held for this application.

11. **Pediatrics**

Pfizer requested a full waiver of pediatric studies for the requested indications and submitted an agreed iPSP in the BLA. Breast and gastric cancers are included in FDA’s September 2005 Guidance (How to Comply with the Pediatric Research Equity Act) for disease-specific waivers. The Pediatric Review Committee met on February 28, 2018 and concurred with the plan for a full waiver. The minutes were entered to DARRTS on March 19, 2018.

12. **Other Relevant Regulatory Issues**

**Application Integrity Policy (AIP)**

The application contained statements from Pfizer that they certified that they did not and will not use in any capacity the services of any person debarred under section 306 of the Federal, Food, Drug, and Cosmetic Act in connection with this application.

**Exclusivity or patent Issues**

*Not applicable.*

**Financial disclosures**

All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the Applicant and propriety interest. Financial disclosure information is
provided for covered studies B3271001, B3271002, B3271004 and B3271006. Certification, using FORM FDA 3454, that none of the financial interests or arrangements described in 21 CFR Part 54 exists, is provided for 858 of the 860 clinical investigators who participated in the covered studies listed above. Two of the 860 clinical investigators listed in the study report had financial information to disclose, which represents 0.2% of the total number of all clinical investigators who participated in the study.

Bioequivalence Inspections

Angel S Johnson from the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated September 14, 2017 and recommended to accept data without a clinical on-site inspection of Pfizer New Haven Clinical Research Unit as this site was recently inspected with the final classification NAI.

Kara A. Scheibner and John A. Kadavil from the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated January 12, 2018 regarding inspections of and Pfizer Inc., Andover, MA. conducted pharmacokinetic (PK) assays for both studies, and neutralizing antibody (NAb) assays for study B3271002. Pfizer Inc., Andover, MA, conducted NAb assays for study B3271001. conducted antidrug antibody (ADA) assays for both studies. No objectionable conditions were observed and Form FDA 483 was not issued during the inspection close-outs at and Pfizer. The final inspection classifications for and Pfizer are No Action Indicated (NAI). However, findings in study reports and observations made during the inspection lead us to recommend exclusion of some data from the studies, because reliability of a portion of the audited studies was impacted. The inspectional findings were isolated in nature and do not impact reliability of all the data.

Mohsen Rajabi Abhari from the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated January 11, 2018. Inspections of studies B3271001 and B3271002 at were conducted. Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI). Significant objectionable conditions were observed during this inspection that impacted the reliability of a portion of the audited studies. However, the inspectional findings were isolated in nature and do not impact the reliability of all the data.

Reviewer Comment: No data was excluded from the analyses of studies B3271002 and B3271001. The recommendation to exclude data was rejected because the inspectional findings were isolated in nature and were not felt to impact the reliability of all the data submitted to the Agency. In addition, the inspection classifications were considered acceptable, and it is unlikely that any of the issues found impacted subject safety or study outcome analysis.
Clinical Inspections

Lauren Iacono-Connors, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from OSI completed the clinical inspection summary (CIS) on March 9, 2018. FDA selected four clinical sites, and a CRO for audit. There were no significant inspectional findings for these 3 clinical investigators. OSI review concluded that the data from Study B3271002 submitted to the Agency in support of BLA 761081, appear reliable based on available information.

Other discipline consults

Tingting Gao and Chi-Ming (Alice) Tu from the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review dated January 31, 2018, that concluded that the proposed proprietary name, TRAZIMERA, was acceptable.

Tingting Gao and Chi-Ming (Alice) Tu from OMEPRM completed a review (dated Feb 28, 2018) that determined that the suffix qyyp for the non-proprietary name is acceptable (trastuzumab- qyyp).

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated March 9, 2018, that defined recommendations relating to carton and container and product labeling.

Pediatric and Maternal Health

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for US-Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and therefore, no registry or pharmacovigilance program is required for this biosimilar. Please refer to the primary clinical/statistical review.

13. Labeling

Proposed labeling submitted by Pfizer was generally consistent with recommendations contained within FDA’s draft Guidance for Industry “Labeling for Biosimilar Products” which recommends that the biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications. Some information of the labeling were revised to reflect PF-05280014 -specific information as well as to comply with current labeling practices. The review teams reserve final comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.
14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action and Risk Benefit Assessment

The Applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The Applicant is seeking licensure for metastatic breast cancer (which was studied in the PF-05280014 clinical program), as well as the adjuvant breast cancer and metastatic gastric cancer indications, which have not been directly studied in the PF-05280014 clinical program. As explained above, extrapolation is scientifically justified.

The data submitted to the 351(k) BLA support a demonstration of biosimilarity for PF-05280014. A demonstration that PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, demonstrating no clinically meaningful differences between the products, support licensure of PF-05280014 as a biosimilar to US-Herceptin under section 351(k) of the PHS Act. Because PF-05280014 is biosimilar to US-Herceptin, PF-05280014 is considered to have a favorable risk-benefit profile for all requested conditions of use.

However, there were several issues with the Drug Substance and Drug Product control strategy, sterility assurance and microbiology product quality. Because of these product quality deficiencies, as summarized in section 3 of this review, this application is not recommended for approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to applicant

See the complete response letter for deficiencies and comments to be communicated to the applicant.

Recommended Regulatory Action

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

/s/

LALEH AMIRI KORDESTANI
04/20/2018