DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761081

COMPLETE RESPONSE

Pfizer Inc.
Attention: Scott C. Anderson, MS
Director, Biosimilars Global Regulatory Affairs
10646 Science Center Drive
San Diego, CA 92121

Dear Mr. Anderson:

Please refer to your Biologics License Application (BLA) dated June 22, 2017, received June 22, 2017, submitted under section 351(k) of the Public Health Service Act for Trazimera (PF-05280014).

We also acknowledge receipt of your amendments dated March 26, 2018, April 10, 2018, and April 17, 2018, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Reference is made to the information and data provided to the Agency concerning the stability of the PF-05280014 Working Cell Bank (WCB) on January 22, 2018 and February 9, 2018. Although the likely root causes for the instability have been identified and corrective actions were implemented in late 2017, the information and data do not support the suitability of the current WCB for commercial production.

   Reference is also made to your response received on February 21, 2018 to Question 1 of the Agency's Information Request (IR) dated February 13, 2018 concerning the PF-05280014 Master Cell Bank (MCB). Because the MCB has undergone extensive transfers since its inception, the information and data provided by the February 21, 2018 response are insufficient to account for the potential impact on MCB stability from these transfers.

   To support a well-controlled and consistent commercial production of PF-05280014, you will need to provide adequate data and information to confirm the stability of the MCB. Once the

stability of the MCB is confirmed, you should qualify a new WCB or validate use of the MCB for commercial production.

2. References are made to your response received on September 22, 2017 to Comment 1 of the Agency's IR dated September 1, 2017, and your response received on February 16, 2018 to Comment 1a of the Agency's IR dated February 9, 2018. The Agency does not agree that the data from the Extractable Content experiment support that the lower limit of the fill weight range used during drug product (DP) manufacturing will result in vials filled with sufficient DP to consistently meet the label claim of 420 mg. The recovery data in the calculations used to support the filling range is based on the average recovery of (b) (4), and not the worst-case recovery of (b) (4) Based on the calculations, a DP vial filled at the lower limit of the fill weight range of (b) (4) recovery would be (b) (4) which would not meet the label claim of 420 mg. Tighten the lower fill weight rejection limit and provide data to support that DP vials filled at the lower fill weight limit can consistently deliver 420 mg of PF-05280014.

3. The information and data provided to support the commercial DP shipping validation do not provide sufficient assurance that the quality of the DP is maintained during commercial shipping and distribution. We have the following comments:
    a. The mechanical performance studies, which include an independent evaluation of vibration and physical shock, are not sufficiently representative of potential stresses induced during routine distribution conditions, where additional factors may contribute stress (e.g., temperature and pressure changes) and multiple stresses could occur concurrently. Therefore, these studies cannot on their own be used in lieu of performing real-time DP shipping validation studies. Provide shipping validation data for the DP from real-time shipping studies or from appropriate simulation studies that are sufficiently representative of the commercial shipping conditions. The data should include an assessment of product quality of pre- and post-shipping DP samples. Include a detailed description of how the study was performed and if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.
    b. It is not appropriate to leverage stability data to support the allowable shipping temperature range of (b) (4), because DP is subjected to additional stresses during shipping, which could potentially impact product stability. To support shipment outside of the validated 2-8°C range, real-time shipping studies or sufficiently representative simulated studies, as described above, should be performed to support the allowable shipping temperature range.
    c. The ability of the passive pallet shipper to maintain the storage temperature of 2-8°C in the actual shipping lanes has not been demonstrated. Provide the shipping validation summary report of the passive pallet shipper in the actual shipping lanes during winter and summer conditions in the BLA resubmission.

4. Implement the following specifications for the control of PF-05280114:
    a. Antibody-dependent cell-mediated cytotoxicity (ADCC) is one of the potential mechanisms of action for trastuzumab. In your response received on February 05, 2018 to Comment 6c of the Agency's IR dated January 17, 2018, a

cell-based FcγRIIIa reporter gene assay was provided as a surrogate assay to assess ADCC activity in the reference material qualifications. Implement this test, or another validated assay, with appropriate acceptance criterion to control for ADCC activity for DS and DP release and stability. The acceptance criteria should be based on product understanding, current process understanding, and clinical experience.

b. As noted in the Agency's IR on November 7, 2017, isomerization of Asp102 (iso Asp102) is shown to impact the potency of trastuzumab. The iso Asp102 is enriched in the B0 peak in CEX-HPLC and the B0 peak of PF-05280114 increases under mild thermal stressed conditions (Section 3.2.S.3.1); therefore, a control strategy for iso Asp102 should be in place to ensure product safety, quality and potency. Given that your current potency assay is not sensitive enough to detect changes in iso Asp102 and it is not appropriate to control iso Asp102 using CEX-HPLC (Refer to IR dated January 4, 2018), an assay should be developed and implemented to control for the level of iso Asp102 for DS and DP release and stability, with appropriate acceptance criterion.

c. As part of the Agency's current considerations regarding the control of effector function, it is understood from publicly available literature that high mannose species contribute to the total level of afucosylated variants. Given the impact of afucosylated variants on potency, we recommend that the total level of high mannose be included as part of the control strategy for the PF-08250114 DS. Implement an appropriate control for high mannose into the DS release specification. The acceptance criteria should be based on the current process understanding and clinical experience.

d. Polysorbate 20 is a critical excipient that can impact product quality and stability. Add testing and quantitative acceptance criteria for Polysorbate 20 to the PF-05280014 DP release specification.

e. Add the test of "extractable content" to the DP release specification with the acceptance criterion of "No less than 420 mg" to ensure that DP lots will meet the label claim.

5. The justifications for specifications provided in Sections 3.2.S.4.5 and 3.2.P.5.6 are not sufficient to support some of the release and end of shelf life acceptance criteria for the PF-05280014 drug substance (DS) and DP. The acceptance criteria for release and end of shelf life should be sufficiently narrow to allow for adequate control of DS and subsequent DP and should be based on your clinical and manufacturing experience. For some product quality attributes that change during storage, it is not appropriate to have the same acceptance criteria for DS and DP release and end of shelf life. The specifications should be set such that materials released at the limit of the acceptance criteria will not result in out of specification results during storage. For some attributes, the DS release and/or end of shelf life specifications should be tighter than those for DP release and/or end of shelf, to avoid DP lots going out of specification. Based on these concepts, the following acceptance criteria should be tightened:

   a. Appearance (Color) for DS release and end of shelf life
   b. Acidic and Basic species by CEX-HPLC for DS and DP release and end of shelf life

6. The additional storages for PF-05280014, as specified in the proposed label, include storage at 30°C for a single period up to 3 months for unopened PF-05280014 or storage at 2-8°C for up to 28 days for PF-05280014 reconstituted in BWFI, within the long-term storage of 48 months at 2-8°C. The information and data provided in the submission are insufficient to support these additional storage conditions. For example, product quality attributes including ADCC (or FcγRIIIa binding) and the levels of iso Asp102 were not assessed to demonstrate that there is no impact on these attributes during these storage conditions. Provide additional information and data to support the proposed additional storage conditions.

7. Method transfer data were provided for the reduced and non-reduced CGE assays from Pfizer St. Louis to Grange Castle; however, no information and data (e.g., from method validation or method transfer) were provided to support that these assays are validated at the Pfizer St. Louis site. Because Grange Castle is the only DP release testing site for these assays (Section 3.2.P.3.1), the method validation for these assays used for commercial DP lot release and stability testing is considered incomplete. Provide information and data to support the method validation of these assays at Pfizer St. Louis.

8. Reference is made to your response received on January 22, 2018 to Comment 1d of the Agency's information request dated December 26, 2017. We disagree with your assessment that the (b) (4) is a low risk operation. As stated in the Agency's IR, (b) (4) represents higher risk for process performance consistency and, subsequently, product quality. Data from commercial scale manufacturing experience and/or process validation that has undergone the (b) (4) operation should be provided to support this process and process controls. Provide information and data to support the proposed (b) (4) operations at scale, or remove the description of (b) (4) operations for the (b) (4) from Section 3.2.S.2.2 of the BLA.

9. Media fill simulations used to validate (b) (4) for PF-05280014 drug product are not included in the BLA. Provide summary data from three media fills performed on fill line (b) (4) in the BLA resubmission.

10. The maximum hold time of PF-05280014 drug produc (b) (4) proposed in the BLA is not supported by relevant microbiology data. Provide summary microbial data from hold time studies conducted in the holding vessels used for PF-05280014 in the BLA resubmission.

11. Capping process parameters for PF-05280014 drug product and BWFI diluent vials do not specify maximum differential forces. Excessive capping differential forces may damage vials and compromise product sterility. For each capper, specify a maximum differential force and provide summary results which demonstrate container closure integrity after capping at a maximum differential force in the BLA resubmission.

12. Vial washing parameters and washing validation summary data are not included in the BLA or in DMF (b) (4). Provide validation summary data and information from three runs performed on each vial washing machine for (b) (4) in the BLA

resubmission. Specify vial washing parameters for PF-05280014 drug product and BWFI diluent vials.

13. Bioburden action limits for PF-05280014 drug product have not been provided for the step [redacted](b) (4). Establish bioburden action limits for this step and provide those limits in the BLA resubmission.

14. The results of the low endotoxin recovery (LER) study performed with the gel clot method are summarized in section 3.2.P.5.3; however, raw data were not provided. Provide the LER study report in the BLA resubmission which describes the method performed and includes raw data (+/- gel clot) to support the reported percent recoveries. Describe the calculations performed to quantify endotoxin. Clarify the type of endotoxin standard used in the LER studies (CSE or RSE) and update section 3.2.P.5.3 accordingly.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, September 18, 2017 which addresses the proposed proprietary name, Trazimera. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update, if appropriate. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
   - Present tabulations of the new safety data combined with the original BLA data.
   - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. The proposed acceptance criteria for the control of size variants, including HMMS by SE-HPLC, Intact IgG by non-reducing CGE, HC+LC and fragments by reducing CGE, for DS and DP lot release and stability are too broad and are not justified based on your manufacturing experience. Provide additional information (e.g., clinical experience) and data (e.g., structure function characterization results) to support the proposed acceptance criteria, or tighten these acceptance criteria to ensure that size variants of PF-05280014 DS and DP are properly controlled.

2. In Section 3.2.S.2.2, the proposed [redacted] rejection limit of [redacted] is not appropriate and does not reflect your current experience for developmental, clinical, and commercial productions. The information and data provided in response to the Agency's IR (Comment 2b; dated December 26, 2017) were based on a small-scale study [redacted] and therefore are insufficient to support the proposed rejection limit. Tighten the rejection limit for [redacted] based on your current manufacturing experience, or provide data generated from the commercial scale process to support the proposed rejection limit.

3. Insufficient information was provided to support the process parameters and acceptable ranges for the [redacted] (Section 3.2.S.2.2). Provide data from process development studies to support these ranges or tighten the operation ranges based on current manufacturing experience and/or process validation studies.

4. Reference is made to your response received on February 21, 2018 to Comment 6c of the Agency's IR dated January 17, 2018. While the validation report (VAL100054746) for the FcγRIIIa reporter gene assay included an assessment of the majority of method validation parameters expected for a potency assay, the stability indicating capacity of this method was not evaluated. We are recommending that ADCC activity of PF-05280014 be controlled for the DS and DP at release and on stability (see CR Comment 4a above under "Product Quality"). If you choose to use your FcγRIIIa reporter gene assay as the means to control for ADCC activity, the stability indicating capability of this assay should be assessed (e.g., by using stressed/forced degraded samples under appropriate conditions). Provide detailed information and data to demonstrate that this method is suitable for its intended use.

5. Reference is made to your response on January 22, 2018 to Comment 8 of the Agency's IR dated December 26, 2017. The overall coverage of the host cell proteins (HCP) recognized by the antibodies in the HCP ELISA [redacted] is poor; therefore, the data and information provided in the IR response is not sufficient to support the use of this assay [redacted] Provide additional information and data to support the coverage of HCP specific for PF-05280014 producing cell line by the anti-HCP antibodies employed in the HCP ELISA.

6. Reference is made to your response on February 05, 2018 to Comment 3b of the Agency's IR dated January 17, 2018. You have agreed to include selectivity criteria to the system suitability criteria for both cation exchange and size exclusion HPLC methods. Provide the updated method description for these methods in the re-submission (e.g., in Section 3.2.S.4.2).

7. Submit product-specific information related to sterilization and depyrogenation validation of containers, closures, and equipment in section 3.2.P.3.5 of the BLA rather than in a Drug Master File.

8. The [redacted] (b) (4) should be included in section 3.2.P.3.4 of the BLA as an acceptance criterion rather than as a control limit.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants," November 2015 at https://www.fda.gov/downloads/drugs/guidances/ucm345649.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Clara Lee, Regulatory Project Manager, at (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Acting Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LALEH AMIRI KORDESTANI
04/20/2018