

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761081Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761081

MEETING MINUTES

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

Dear Mr. Anderson:

Please refer to your Biologic License Application (BLA) submitted under section 351(k) of the Public Health Service Act for PF-05280014.

We also refer to the meeting between representatives of your firm and the FDA on June 21, 2018. The purpose of the meeting was to obtain clarification regarding the product quality items identified in the complete response letter dated April 20, 2018.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Fatima Rizvi, Regulatory Project Manager, at (240) 402-7426.

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Fatima Rizvi, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 1

Meeting Date and Time: June 21, 2018 3:30 PM – 4:30 PM
Meeting Location: White Oak Building 22, Conference Room 1315

Application Number: BLA 761081
Product Name: PF-05280014
Proposed Indication: Same indications as approved for US-licensed Herceptin
Sponsor/Applicant Name: Pfizer Ireland Pharmaceuticals

Meeting Chair: Laleh Amiri Kordestani, MD
Meeting Recorder: Fatima Rizvi, PharmD

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Acting Supervisory Associate Director, DOP1
Nancy Scher, MD, Clinical Reviewer, DOP1
Rachel Novak, PhD, Lead Product Quality Reviewer, OBP
Virginia Carroll, PhD, Quality Microbiology Reviewer, OBP
Maria Candauchacon, Quality Assessment Lead, DMA, Branch IV
Michele K. Dougherty, PhD, Science Policy Analyst, OND/TBBS
Yu-Yi Hsu, PhD, CMC Biostatistic Reviewer/OTS/OB/OBVI
Tyree Newman, Senior Regulatory Project Manager, OND/TBBS
Claudia, MS, PhD, Pharmacologist/Toxicologist Reviewer, DHOT
Hui Zhang, PhD, Biostatistics Reviewer, DBV
Marlene Schultz-Depalo, MS, MA, RAC, Biosimilar Program and Policy Analysis, OBP
Fatima Rizvi, Pharm D, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Raj Aggarwal, PhD, Senior Director, Safety Risk Lead
Martin Allen, PhD, Senior Director, Bioprocess Research and Development
Scott Anderson, MS, RAC, Director, Global Regulatory Affairs
Rodney Combs, PhD, A.R. Fellow, Bioprocess Research and Development
Marya Czupryn, PhD, Vice President, Scientific Strategy, Biotherapeutics Pharm. Sciences
Jerry (Xiaoming) Huang, MS, Director, Global Regulatory Affairs – Regulatory CMC
Carol Kirchhoff, PhD, Biotechnology and Aseptic Sciences
Kristine McCarthy, PhD, Science Principle Scientist, Bioprocess Research and Development
Joe McClellan, PhD, Vice President Biosimilar Development

Paul Mensah, PhD, Vice President, Bioprocess Research and Development
Trina Quintana, Senior Manager, Global Regulatory Affairs
Julie Ann Rosenberg, MD, Senior Director, Asset Lead Biosimilar Development
Tanya Shang, PhD, Senior Director, Analytical Research and Development
Lisa Skeens, PhD, Vice Present, Global Regulatory Affairs
Alexandra Thiele, PhD, Senior Director, Biosimilars Clinical
Chandra Webb, SB, A.R. Fellow, Pharm Research and Development
Craig Whitehead, PhD, Vice President, Global Regulatory Affairs

1.0 BACKGROUND

Pfizer requested a BPD Type 1 meeting to obtain clarification and gain alignment with the Agency to ensure Pfizer's BLA resubmission will fully address Product Quality items identified in the FDA's Complete Response Letter dated April 20, 2018. PF-05280014 is a recombinant humanized IgG1 monoclonal antibody (mAb) directed against the human epidermal growth factor receptor 2 (HER2/neu receptor). The proposed name is Trazimera (trastuzumab-qyyp). PF-05280014 is being developed as a proposed biosimilar to US-licensed Herceptin under IND 110,428.

In Pfizer's response to the Complete Response Letter, data and information regarding product quality deficiencies related to the stability of the Master Cell Bank (MCB) and Working Cell Bank (WCB), the control strategy for the Drug Product (DP) fill weight and extractable volume, shipping validation for the commercial DP, the strategy for controlling isoAsp102 and high mannose species and data from microbial hold time studies were provided.

FDA sent Preliminary Comments to Pfizer Ireland Pharmaceuticals, Inc on June 19, 2018.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Pfizer Ireland Pharmaceuticals and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1: Is the provided data set adequate to assess the stability of the MCB and therefore the MCB suitability for establishing a new Working Cell Bank?

FDA Response to Question 1: Yes, the Agency agrees that data appear adequate to assess the stability of the MCB.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion

Meeting Discussion: None

Question 2: Does the Agency agree that the data provided for WCB vials stored at (b) (4) are adequate to allow the continued use of these WCB vials at (b) (4) for commercial production while the new WCB is being qualified?

FDA Response to Question 2: The Agency agrees that the vials of WCB (b) (4) stored at (b) (4) appear to have been moved to (b) (4) prior to the sub-optimal handling of the WCB vials currently stored at Andover and Grange Castle. Regarding the use of the WCB vials at (b) (4) for use in commercial manufacturing, the Agency does not object to their use. Please clarify how you intend to manage the WCB supply and qualification of a new WCB to ensure there is no disruption to the market supply of PF-05280014.

Sponsor's Response dated June 21, 2018: Pfizer would like to describe the planned management of the current WCB (WCB (b) (4)) vials stored at (b) (4) and qualification of new WCB (W38320) to ensure there is no supply disruption to the market supply PF-05280014:

1. The current WCB (WCB (b) (4)) vials at (b) (4) will maintain supply of drug substance for drug product manufacture into, at least, (b) (4).
2. The updated protocol for the qualification of the new WCB (W38320) (see response to question 3 below) will be provided within the resubmission.
3. The qualification of the new WCB (W38320) will be completed (b) (4).
4. These activities will ensure that supply continuity of PF-05280014 will be maintained.

Meeting Discussion: The Agency expressed concern that the proposed manufacturing schedule for ensuring that there would not be a disruption in the manufacture of PF-05280014 is under the assumption that no deviations or unexpected issues occur; however, the overall strategy appears reasonable. The sponsor asked if it would be acceptable to begin the qualification of the new WCB prior to the approval of the WCB protocol that will be submitted as part of the Complete Response submission. The Agency stated that this could pose a risk in the case that the WCB protocol is not adequate.

Question 3: Does the Agency agree with Pfizer's updated WCB qualification protocol (Section 14.1 Appendix 1), (b) (4)

FDA Response to Question 3: No, the Agency does not agree that the protocol is sufficient or complete. No information was provided on the assessment of product quality or the acceptance criteria that will be used to assess the lots manufactured with the new WCB. Note that the acceptance criteria should be sufficiently narrow (e.g. not just "meets release criteria") and should be assessed against historical data. In addition, no data was provided in the original BLA submission or the meeting package to support the rejection limit for (b) (4)

Remove this limit from the protocol or provide appropriate data to support that (b) (4) will not impact the manufacturing process or

product quality. A final determination of the adequacy of the protocol will be a review issue.

If you intend to perform the at-scale qualification at a site other than (b) (4) the information for qualification of the new WCB (and the additional information discussed in FDA Response to Question 4 below) will need to be included with the resubmission and approved by the Agency prior to use of the new WCB to ensure consistent manufacture of PF-05280014 (see FDA Response to Question 2 above).

Sponsor's Response dated June 21, 2018: The protocol for the new WCB (W38320) qualification will be updated to include:

1. Product quality assessment will be conducted using acceptance criteria established on the basis of the statistical range of historic data, which will be specified within the protocol for WCB (W38320).
2. Details of the product quality assessment will include an assessment of drug substance product-related CQAs: identity, potency (inhibition of cell growth and ADCC), protein concentration, appearance, pH, charge heterogeneity, N-linked glycan profile, monomer, HC+LC, HMMS, fragments.
3. Drug substance process-related CQAs (HCP and residual DNA) will also be assessed.
4. The (b) (4) rejection limit will be adjusted to (b) (4). This is in agreement with the (b) (4) WCB renewal qualification protocol as well as a statistical analysis of the (b) (4) data from the commercial scale experience.

With the addition of the items outlined above, Pfizer will include the updated protocol for WCB (W38320) in the resubmission (b) (4)

Meeting Discussion: The Agency agreed that the additional information provided appears reasonable, but the adequacy of the final protocol will be reviewed upon resubmission of the BLA. The Agency agreed that qualification of the new WCB including 3 at-scale runs is acceptable. The Agency also stated that the expectation is that the acceptance criteria for the WCB qualification protocol be sufficiently narrow to be able to detect changes in product quality or process consistency and that it may not be acceptable for the acceptance criteria to be the same as the release criteria for important quality attributes. Justification for the acceptance criteria should be provided in the submission. The Agency noted that any updates to the control strategy that are submitted or agreed to as part of the BLA resubmission review should be incorporated into the WCB protocol, as appropriate. The tightening of the (b) (4) appears reasonable. Upon approval of the WCB qualification protocol, (b) (4)

Question 4: The new WCB batch W38320 has been tested in accordance with WCB specifications and genotypic comparability to the MCB has been confirmed (data presented in Table 10 and Table 11). The remaining component of the proposed WCB qualification protocol is process performance confirmation at commercial scale. The commercial manufacturing facility for PF-05280014 is contract manufacturer (b) (4) and there is the potential that facility time may not be available for Pfizer to execute the process performance component of the qualification protocol for the new WCB. Pfizer proposes to perform the at scale process performance confirmation at either (b) (4) or a Pfizer commercial facility in Grange Castle, which is capable of running the proposed commercial process for PF-05280014. Is this approach for the qualification of W38320 acceptable to the Agency?

FDA Response to Question 4: The Agency recommends that the at-scale performance qualification of the new WCB be performed at (b) (4). Qualification of a new WCB at a different manufacturing facility could be challenging if the manufacturing process, equipment and facility are different.

However, it could be acceptable to perform the at-scale qualification studies for the new WCB at the Grange Castle site, if the Grange Castle site is highly equivalent to the manufacturing site at (b) (4) (e.g. scale, equipment, set-up, etc.). This information should be provided in the resubmission in a side by side comparison for the Agency to review. In addition, comparability studies should be performed to demonstrate that the lots manufactured with the new WCB at Grange Castle are comparable to the historical lots manufactured at (b) (4). Please note, unless Grange Castle is intended to be added to the license, you will not be able to release the lots manufactured at Grange Castle.

Sponsor's Response dated June 21, 2018: Pfizer appreciates the FDA clarification regarding the use of Grange Castle for the qualification of a new WCB. Pfizer confirms that we intend to qualify WCB W38320 at (b) (4).

Meeting Discussion: The Agency stated its recommendation that Pfizer perform the at-scale qualification runs for the new WCB at (b) (4).

Question 5: Does the Agency agree that the fill weight rejection limit as proposed is appropriate?

FDA Response to Question 5: Yes, the Agency agrees the current strategy is appropriate.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion.

Post meeting clarification: Regarding the question posed on June 25, 2018 (via email), the Agency would like to clarify that the current strategy specified in the initial BLA, control fill weight limits of (b) (4) with a target fill weight of (b) (4) is acceptable.

Question 6: Does the Agency agree that the existing control strategy to ensure the label claim of 420 mg is sufficient and that an extractable content specification is not warranted? Alternatively, does the Agency agree that if an extractable content specification is implemented, it is appropriate for the method to use the actual protein concentration measured concurrently and not use the nominal protein concentration?

FDA Response to Question 6: Yes, based on the information provided in the meeting package, the Agency agrees that extractable volume is not needed at release of the PF-05280014 drug product.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion.

Meeting Discussion: None

Question 7: Does the Agency agree that the information outlined regarding shipping validation will be suitable to support the resubmission of the BLA?

FDA Response to Question 7: In the BLA resubmission, include the shipping validation summary and report for the passive pallet shipper using the actual shipping lanes during winter and summer conditions to demonstrate the ability of the shipper to maintain 2-8°C. Describe the loads and the number and location of temperature monitors. Include an acceptance criterion for duration of shipment.

Regarding the allowable shipping temperature range of (b) (4) the Agency does not agree that stability data can be leveraged to support temperature excursion during real-time shipping because the drug product is exposed to different stresses that could impact product quality. It may be possible to leverage data from the mechanical performance studies, if testing was performed outside of the intended shipping temperature of 2-8°C, if the mechanical performance study is sufficiently representative of real-time shipping conditions and the appropriate product quality attributes are tested.

Sponsor's Response dated June 21, 2018: Pfizer acknowledges the Agency's feedback and we propose to provide the following comprehensive data package to support product shipment:

Pfizer intends to provide the following information in the BLA resubmission in support of shipping of drug product:

1. Report for the operational qualification of the (b) (4)
2. Report for the operational qualification of the passive pallet shipper (passive) used for transport from the (b) (4) to the US distribution centers covering both the summer and winter temperature profiles.

3. Report for the performance qualification of the [REDACTED] (b) (4) using a representative product as a representative load.
4. Reports for the performance qualification of the passive pallet shipper used for transport from the [REDACTED] (b) (4) to the US distribution centers covering both the summer and winter temperature profiles, using a representative product as a representative load and a representative shipping lane, including a supportive rationale document.
5. Report for the simulated shipping study [REDACTED] (b) (4)
6. Report for an additional simulated shipping study of packaged drug product

In response to comments on the passive pallet shipper, Pfizer acknowledges the Agency's feedback and will include reports for the passive pallet shipper transported during winter and summer conditions to demonstrate the ability of the shipper to maintain 2-8 °C using a representative product as the representative loads in a representative shipping lane. In addition to the passive pallet shipper performance qualification reports, Pfizer will provide documented rationale of the applicability to PF-05280014 in the BLA resubmission.

[REDACTED] (b) (4)

An assessment of the shipping lane used for the performance qualification demonstrates that the shipping lane qualified in the aforementioned reports [REDACTED] (b) (4) is representative of the shipping lanes to be used for PF-05280014 [REDACTED] (b) (4). These lanes involve the same geographic regions, similar exposure temperatures, numbers of handovers, exposure to road and air transport stresses, durations of transport legs, and overall transit time.

The acceptance criterion for duration of shipment for the performance qualification was based on the results of the operational qualification.

In response to comments on simulated shipping studies Pfizer acknowledges the concern regarding support for the temperature range, and would like to reiterate that the intended shipping temperature is 2 – 8 °C. Time out of refrigeration during pallet packing and similar operations is controlled.

Pfizer acknowledges the concerns regarding concurrent stresses during shipment and intends to conduct an additional simulated shipping study as outlined below, to augment the data obtained from the studies that have already been conducted. The additional simulated shipping study is intended to challenge the product under conditions representing global shipping, including challenging temperature ranges, mechanical stress such as vibration, and pressure. The figure below provides a high level depiction of the global transport simulation lane showing mode of transportation and duration:

(b) (4)



(b) (4)

Meeting Discussion: The Agency indicated that the approach appeared to be acceptable. The Agency also stated that qualification of the (b) (4) is an inspectional issue and does not need to be included in the BLA resubmission.

Question 8: Does the Agency (b) (4)

If not, can the Agency please further clarify what additional conditions besides impact, vibration, temperature would be experienced during shipment that could impact drug product quality?

FDA Response to Question 8: No, the FDA does not agree. No additional information was provided in the meeting package for the Agency to assess how the mechanical performance studies are representative of real-time shipping conditions. As stated in the Complete Response letter, in the resubmission, provide a detailed description of how the mechanical performance studies were executed including, but not limited to, the parameters tested, temperature at which they were tested and duration of the conditions tested. In addition, provide a justification for how Pfizer believes that these conditions are sufficiently representative of real-time shipping conditions. As an additional level of support, it may be possible to leverage the shipment of test samples, if they were shipped to an alternate site for testing.

Sponsor's Response dated June 21, 2018: As detailed above in the response to question 7, Pfizer is planning to complete an additional simulated shipping study and include the report in the BLA resubmission. This study will be performed on packaged drug product, will include exposure to (b) (4) and include the parameters and durations as detailed in response to question 7. This study will complement the mechanical performance studies that were conducted at ambient temperature.

Pfizer acknowledges the suggestion to leverage the shipment of test samples.

Meeting Discussion: The Agency stated that Pfizer should provide sufficient detail on the study design for the simulated shipping studies and justification to support that the conditions used in all simulated studies are sufficiently representative of real-time shipping conditions. Justification should also be provided for the product quality attributes that are assessed in the study.

Question 9: What, if any, additional drug product quality attributes other than Container Closure Integrity (CCIT) are expected to be considered?

FDA Response to Question 9: In addition to product attributes assessed in the BLA submission and CCI, provide an analysis of any damage that was recorded to the drug product primary and secondary packaging during the mechanical performance studies.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion.

Meeting Discussion: None

Question 10: Does the Agency agree that Basic species CEX-HPLC release and stability acceptance criteria for DS and DP, in addition to LC/MS/MS peptide mapping (b) (4) are appropriate for the control of isoAsp102?

FDA Response to Question 10: No, the Agency does not agree. Insufficient information was provided to demonstrate that measurement of total basic species is sensitive enough to detect small changes in isoAsp102 levels. For example, the study provided in Table 15 of the meeting package comparing the levels of total basic peaks, the B0 peak and isoAsp102 only had two time points. This is not adequate to demonstrate that changes in these peaks occur at similar time points and rates. More frequent and earlier time points would be more informative. To be able to show that the measurement of basic species is sufficient to control the levels of isoAsp102, data should be provided to demonstrate that detection of basic peaks by CEX-HPLC can detect small changes in isoAsp102 under all relevant stress conditions that are likely to be encountered during normal manufacturing and storage.

Sponsor's Response dated June 21, 2018: We acknowledge and appreciate FDA's advice. Additional studies will be performed to assess the sensitivity of the CEX-HPLC (via total basic species) to small changes in isoAsp102 levels under relevant stress conditions likely encountered during normal manufacturing and storage.

- Examples of additional studies include: multiple interim time points will be assessed under conditions that induce isomerization to further evaluate correlation between basic species levels and isoAsp102 levels; spike studies using materials enriched with isoAsp102 to further assess sensitivity of CEX-HPLC

A comprehensive data package will be included in the resubmission to support the control of isoAsp102 by CEX-HPLC basic species.

If the results do not support the ability of CEX-HPLC to detect isoAsp102 level under relevant stress conditions likely encountered during normal manufacturing and storage, Pfizer will commit to develop and implement a specific isoAsp102 method for release and stability testing of commercial DS and DP.

Meeting Discussion: The Agency stated that it may be possible to control isoAsp102 levels by CEX-HPLC; however, sufficient data should be provided in the resubmission to demonstrate the CEX-HPLC method is capable of detecting small changes in isoAsp102 levels under conditions that the product may encounter during typical manufacturing and storage. Based on the results of the additional analyses, if a new method is to be implemented to control isoAsp102 levels, the new method may be implemented as part of a post-marketing commitment.

Question 11: Does the Agency agree with Pfizer's proposal to implement a drug substance release specification for total afucosylated species as an appropriate control for high mannose?

FDA Response to Question 11: No, the Agency does not agree. High mannose forms have been shown in publicly available literature to clear more quickly than other afucosylated species, which may affect the PK and subsequently the efficacy of PF-05280014. Provide a control strategy for controlling the levels of high mannose in the resubmission.

Sponsor's Response dated June 21, 2018: We acknowledge the Agency's suggestion and we will establish an acceptance criteria for high mannose and update the control strategy in the resubmission.

Meeting Discussion: None

Question 12: Is it acceptable to the Agency to further update the process description in the BLA resubmission such that there is a [REDACTED] (b) (4)

FDA Response to Question 12: Yes, the process description may be updated, provided that the supporting data for the change is submitted to the BLA and the description of the original process used for the three process validation lots manufactured in 2015 is included.

Sponsor's Response dated June 21, 2018: Pfizer acknowledges Agency's feedback and will provide the appropriate dataset to fully support the updated process description.

The description of the original process used for the three process validation lots manufactured in 2015 will be retained in the BLA resubmission, together with the process validation data generated with the updated process to include a [REDACTED] (b) (4). To support the updated process description, Pfizer will present the following data for three lots of PF-05280014 drug product in the BLA resubmission. The tests were selected based on a risk assessment of the process change.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for their response and we require no further discussion.

Meeting Discussion: None

Question 15: Is it acceptable to the Agency to provide the annual DSUR (25 May 2018) as the requested safety update with the resubmission?

FDA Response to Question 15: No. Please refer to the Safety Update requirements detailed in the Complete Response Letter dated April 20, 2018.

Sponsor's Response dated June 21, 2018: The Agency requested a Safety Update to be provided with the resubmission in the Complete Response Letter of April 20, 2018.

One clinical study, B3271002, presently continues. While the study reached all clinical endpoints by Week 53, limited safety data are still collected among 96 patients who continue to receive treatment under during the extension period (Protocol Amendment 4, submitted to the FDA as part of the 120 Day safety update).

Below is Pfizer's proposal to address the Agency's CRL:

FDA Safety Update Request from April 20, 2018 Complete Response (CR) Letter	Pfizer Proposal to Address Request
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.	Any new safety findings or any significant changes from previous findings will be described in the safety update in the BLA resubmission.
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.	Comparison of 120 day safety update vs. B3271002 safety data will be provided in the safety update for discontinuations due to AE, SAEs, and common AEs.
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.	No studies have been completed since the BLA submission.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study	These case report forms and narratives for the B3271002 study will be provided in the BLA resubmission.

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.	Any new safety findings or any significant changes from previous findings will be described in the safety update in the BLA resubmission.
6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).	Updated exposure data from B3271002 study will be provided in the BLA resubmission.
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.	This information cannot be provided since the product will not be launched in any country at the time of BLA resubmission.
8. Provide English translations of current approved foreign labeling not previously submitted.	Pfizer has received a CHMP positive opinion, with EU approval anticipated by Aug 2018, at which time Pfizer will provide the EU SmPC.

Meeting Discussion: None

Question 16: Please confirm if the planned approach to responding to each deficiency is acceptable to support the Complete Response submission to the 351 (k) BLA.

FDA Response to Question 16: No. In addition to responding to the Complete Response letter in module 1, you will need to update all appropriate modules in your resubmission.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion.

Meeting Discussion: None

Question 17: Does Pfizer need to resubmit the proposed suffixes for review as part of the resubmission?

FDA Response to Question 17: No, you do not need to resubmit the proposed suffixes for review as part of the resubmission. The acceptability of your proposed and conditionally accepted suffix, -qyyp, will be re-evaluated when you resubmit your BLA. If we find the suffix unacceptable upon our re-evaluation, we will inform you of our finding.

Sponsor's Response dated June 21, 2018: Pfizer would like to thank the Agency for the response and we require no further discussion.

Meeting Discussion: None

3.0 ADDITIONAL INFORMATION

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

Meeting Slides attached

17 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FATIMA M RIZVI
07/19/2018

LALEH AMIRI KORDESTANI
07/20/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110427

MEETING MINUTES

Pfizer, Inc.
Attention: Scott C. Anderson, MS, RAC
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Mr. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-05280014.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2017. The purpose of the meeting was to discuss the overall content and format of your planned 351(k) Biologics License Application (BLA) for PF-05280014.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-5364 or email me at sakar.wahby@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sakar Wahby, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
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Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: Biosimilar Biological Product Development (BPD) Type 4

Meeting Date and Time: February 7, 2017; 10:00 AM- 11:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 110427
Product Name: PF-05280014
Indication: PF-05280014 is being developed for the same indications as approved for US-licensed Herceptin
Sponsor/Applicant Name: Pfizer Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Sakar Wahby, PharmD

FDA ATTENDEES

Amna Ibrahim, MD, Deputy Director, Division of Oncology Products 1 (DOP1)
Julia Beaver, MD, Associate Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Genevieve Schechter, MD, Medical Officer, DOP1
Lynn Howie, MD, Medical Officer, DOP1
Tsong, Yi, PhD, CMC Statistics Team Leader, OB/DBVI
Meiyu Shen, PhD, CMC Statistics Team Leader, OB/DBVI
Chao Wang, PhD, CMC Statistics Reviewer, OB/DBVI
Tsong Yi, PhD, Division Director, OB/DBVI
Shenghui Tang, PhD, Statistics Team Leader, DBV
Stella Karuri, PhD, Statistics Reviewer, DBV
Sarah Kennett, PhD, Review Chief, DBRR I, OBP
Kevin Li, PhD, Primary CMC Reviewer, DBRR I, OBP
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
Kimberly Ringgold, PhD, Pharmacology/Toxicology Reviewer, DHOT
Runyan Jin, PhD, Pharmacology Reviewer, Office of Clinical Pharmacology, DCP5
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Marlene Schultz-Depalo, MS, MA, RAC, OBP Biosimilar Program Analyst, CDER/OPQ/OBP
Sakar Wahby, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Raj Aggarwal, PhD, Senior Director, Safety Risk Lead
Scott Anderson, MS, RAC, Director, Global Regulatory Affairs
Riddhi Dedhia, MS, MBA, Senior Manager, Global Regulatory Affairs
Trina Quintana, Manager Global Regulatory Affairs
Fiona Hilton, MSc, CStat, Director of Statistics
Jerry (Xiaoming) Huang, MS, Global Regulatory Affairs - Regulatory CMC
Ira Allen Jacobs, MD, JD, MBA FACS, Global Medical Affairs
Carol Kirchhoff, PhD, Biotechnology and Aseptic Sciences
Robert Wolk, MD, Global Clinical Lead, Submissions-Biosimilars
Charles Zacharchuk, MD, PhD, Clinical Research, Oncology
Bharat Damle, Senior Director Global Clinical Affairs

1.0 BACKGROUND

Purpose of the meeting is to discuss the planned submission in June, 2017 of Biologics License Application (BLA) for PF-05280014 (proposed name: TRAZIMERA) using the 351(k) pathway. PF-05280014 is a proposed biosimilar to US-licensed Herceptin (trastuzumab).

Proposed indications for PF-05280014 include:

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

Pfizer is developing PF-05280014 in a stepwise comparison approach demonstrating similarity of the Pfizer product to the reference product using Quality/Chemistry, Manufacturing, and Control (CMC), nonclinical, and clinical studies. Previous interaction with the Food and Drug Administration (FDA) include two meetings held on April 13, 2011 and February 10, 2012 where the proposed clinical program comparing PF-05280014 (150 mg/ vial presentation) and EU-approved trastuzumab (150 mg/vial) was discussed and whether the comparison of those two presentations would be acceptable to support licensure of PF-05280014 (440 mg/vial presentation) in the US under the 351(k) pathway. FDA agreed in principle to that approach provided that adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity is submitted, an acceptable scientific bridge to the US-licensed reference product is established, and that the comparability of the 150 mg/vial and the 440 mg/vial presentations of PF-05280014 is established. A BPD Type 3 meeting was

held on July 12, 2013 to discuss data to support the proposed bridge to US-licensed Herceptin, and the comparability study results for Pfizer's 150 mg and 440 mg presentations. Two additional meetings, both BPD Type 2, were held on January 8, 2014 and September 1, 2015.

CMC Strategy: To date, a total of 138 lots of US-licensed Herceptin and EU-approved trastuzumab have been analyzed. Eleven (11) batches of PF-05280014 drug substance have been manufactured including 8 batches at the intended commercial production scale and manufacturing facility and 3 representative development batches on a smaller scale. In addition, 13 lots of drug product have been manufactured at the intended commercial production scale and manufacturing facility.

Non-Clinical Strategy: The nonclinical toxicology program consisted of a GLP compliant single-dose intravenous (IV) toxicokinetic study in male mice to compare the effects of PF-05280014 to those of US-licensed Herceptin and EU-approved trastuzumab. This single dose study was designed to fully characterize the pharmacokinetic profile and non-target mediated clearance, minimize potential for immunogenicity in a non-pharmacologically relevant species, and support the single dose in the male healthy volunteers study. This single nonclinical study was deemed sufficient as no toxicologic responses were reported in the originator nonclinical program and no relevant animal model or suitable pharmacodynamic endpoints exist to accurately compare the *in vivo* behavior of PF-05280014 and the reference product. A repeat-dose toxicity study was requested by the PMDA to assess for potential toxicities associated with possible impurities in PF-05280014. A GLP compliant, 2-week repeat-dose IV toxicity and toxicokinetic study with PF-05280014 alone was conducted in male and female mice. The 2-week, non-comparative, repeat-dose toxicity study in male and female mice did not show any test article-related effects for PF-05280014.

Clinical Development: Study B3271001 is a 3-way comparative pharmacokinetic study using US-licensed Herceptin, EU-approved trastuzumab and PF-05280014. Preliminary results indicate pharmacokinetic similarity for PF-05280014 to both US-licensed Herceptin and EU-approved trastuzumab and for EU-approved trastuzumab to US-licensed Herceptin. No evidence of immunogenicity was observed in this single dose study. Due to a numerical (but not statistical) difference in the incidence of pyrexia an additional clinical trial (Study B3271006) was performed which showed no difference in the incidence of fever with PF-05280014 administration. To evaluate similarity of the safety profile, efficacy, and immunogenicity a multicenter, double-blind, randomized clinical trial evaluating the safety, efficacy, pharmacokinetics, and immunogenicity of PF-05280014 plus paclitaxel versus EU-approved trastuzumab plus paclitaxel for the first-line treatment of patients with HER2-positive metastatic breast cancer is being conducted.

Status of PF-05280014 U.S. Clinical Development Program (Table 2 in briefing book)

Study	Study Title/Description	Status	Actual Number of Patients Randomized	Proposed Commercial Formulation
B3271001	Phase 1, Double-Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-05280014 and Trastuzumab sourced from US and EU administered to Healthy Male Volunteers	Completed	105	Yes
B3271006	A Phase 1, Double-Blind, Randomized, Parallel-Group, Single-Dose, 2-Arm, Safety Study of PF-05280014 and Trastuzumab Sourced from the US Administered to Healthy Male Volunteers	Completed	162	Yes
B3271002	A Phase 3 Randomized, Double-Blind Study of PF-05280014 Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel for the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer	Enrollment complete; clinical conduct ongoing	707	Yes
B3271004	A Randomized, Double-Blind Pharmacokinetic Study of PF-05280014 Plus Taxotere® and Carboplatin Versus Herceptin® Plus Taxotere® and Carboplatin For the Neoadjuvant Treatment of Patients with Operable HER2- Positive Breast Cancer	Completed	226	Yes

Study B3271002 is an ongoing randomized, double-blind study comparing the safety, efficacy, pharmacokinetics (PK) and immunogenicity of PF-05280014 in combination with paclitaxel versus EU-approved trastuzumab with paclitaxel in patients with HER2-positive, metastatic breast cancer in the first-line treatment setting. The primary objective is Objective Response Rate (ORR) at Week 25 and confirmed by central radiologic response within the intent-to-treat (ITT) population with a pre-specified equivalence interval of 0.80-1.25. Patients were stratified by prior trastuzumab exposure (yes or no) and estrogen receptor status (ER+ or ER-). Seven hundred seven (707) patients from 156 sites in 24 countries were randomized and 702 women were treated. Five randomized patients were enrolled but not treated. At the time of data cut-off, 17 patients had completed the study, 127 had discontinued (43 during treatment, 84 during long

term follow-up), and 558 are ongoing. On the PF-05280014 arm 46.9% of participants discontinued while on the EU-approved trastuzumab arm 48.7% discontinued. The following table shows the ORR for each arm by central radiologic review.

Objective Response Rate based on Central Radiology Review – ITT Population (Table 2, in Appendix 2 of briefing book)

Endpoint	PF-05280014 (N=352)	Trastuzumab-EU (N=355)	Risk Ratio	95% CI
CR (n, %)	10 (2.8%)	13 (3.7%)	0.776	(0.352, 1.710)
PR (n, %)	210 (59.7%)	223 (62.8%)	0.950	(0.844, 1.068)
ORR (n, %)	220 (62.5%)	236 (66.5%)	0.940	(0.842, 1.049)
95% CI				

The observed risk ratio was 0.94 for PF-05280014 over EU-approved trastuzumab with 95% CI of 0.842-1.049. No clinical or statistical differences were observed in the secondary endpoints of: duration of response (DOR); 1-year progression-free survival (PFS); and, the one year survival rate (overall survival; OS). Fifty-one deaths (14.6%) were reported on the PF-05280014 arm and 54 (15.3%) deaths on the EU-approved trastuzumab arm. Adverse events and serious adverse events were balanced between arms. One patient on the EU-approved trastuzumab arm tested positive for anti-drug antibodies, while none on the PF-05280014 arm were positive. At the time of submission of the BLA approximately 80% of patients will have completed one year on study treatment.

The 120 day safety update (single supplemental CSR) with a data-cut off of January, 2017 will include 100% of patient data supporting the secondary endpoints for up to one year of treatment. Data post week 53 will not be analyzed or submitted to the BLA.

In addition a final Clinical Study Report for Study B3271004 will be included in the BLA submission per agreement reached on March 22, 2016.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Pfizer and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

FDA sent Preliminary Comments to Pfizer Inc. on February 3, 2017. Pfizer Inc. sent responses to FDA Preliminary Comments on February 6, 2017.

2.0 DISCUSSION

Question 1:

Does the FDA have any feedback regarding the proposed structure and format of the trastuzumab 351(k) BLA as presented in Appendix 3 such that it meets the Agency's expectations for e-CTD submission?

FDA Response:

Refer to Section 3 of this document under SUBMISSION FORMAT REQUIREMENTS.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

The Agency informed the Sponsor that CMC information should not be included in the 120 day safety update. Sufficient stability data to support analytical similarity, any relevant comparability, and setting an appropriate expiry period should be included in the initial BLA submission. Insufficient stability data is considered a potential filing issue.

The Sponsor inquired whether they can use comparability data to support using stability data for drug substance stored in cryovessels to set an expiry period for drug substance stored in bags. The Agency's expectation is that the stability data to support expiry dating be obtained from material stored in the intended commercial container closure. The Agency will provide comments, if needed, following review of data and proposals regarding expiration dating submitted in the BLA.

Question 2:

Does the FDA have any feedback regarding the general location of specific comparative data content (analytical, nonclinical and clinical) across the BLA including a summary of the totality of evidence in e-CTD Module 2.2 *Introduction* in support of the demonstration of biosimilarity between PF-05280014 and the trastuzumab reference product?

FDA Response:

No.

Pfizer Reply:

Pfizer would like clarification that "No" means that the Agency agrees with Pfizer's proposal and has no concerns with the approach to include a summary of the totality of evidence in e-CTD Module 2.2 *Introduction* in support of the demonstration of biosimilarity between PF-05280014 and the trastuzumab reference product?

Meeting Discussion:

The Agency agreed with Pfizer's proposal and had no concerns with this approach.

Question 3:

Does the Agency have any feedback on the approach for an overview of regulatory requirements from Section 351(k) of the PHS Act ("351(k) roadmap") as presented in Appendix 4.

FDA Response:

The approach is reasonable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 4:

Does FDA have additional comments on the adequacy of the proposed structure of the BLA to support the review?

FDA Response:

Please refer to the Product Quality Microbiology Additional Comments at the end of the document for the location of microbiology related information.

Pfizer Reply:

Pfizer acknowledges the Agency's comment. All the points noted in the FDA Microbiology comments will be addressed. No further discussion is required.

Meeting Discussion:

No discussion occurred.

Question 5:

Does the Agency have any feedback on the Sponsor's plans to follow previous advice and provide a simplified Module 2.5 that is adjusted for biosimilar content and refers the reviewer to the content of Module 2.7 summaries?

FDA Response:

No.

Pfizer Reply:

Pfizer would like clarification that "No" means that the Agency agrees with Pfizer's proposal and has no concerns with the approach to include a simplified mapping document within Module 2.5 that refers the reader to the relevant Module 2.7 summaries that will detail the safety, efficacy, PK and immunogenicity information for the submission?

Meeting Discussion:

The Agency agreed with Pfizer's proposal and had no concerns with this approach.

Question 6:

Does FDA have any feedback with the proposed labeling concept for trastuzumab to support the BLA submission?

FDA Response:

We note that your proposed approach will be to use (b) (4)

excepting sections noted. This approach is not consistent with the recommendations conveyed in the draft guidance for industry, *Labeling for Biosimilar Products*¹, regarding terminology for product identification. Product identification will depend on the information being described, and not every section of the PF-05280014 labeling will be (b) (4)

Pfizer Reply:

Pfizer acknowledges the Agency's response and plans to follow the draft guidance for industry, "Labeling for Biosimilar Products". No further discussion is required.

Meeting Discussion:

No discussion occurred.

Question 7:

Pfizer understands in accordance with current guidance that biosimilar labels will not contain information that supports the assessments of biosimilarity. It remains important to proactively share information that supports the assessments of biosimilarity with prescribing HCPs. Does FDA have any feedback on this topic which may inform development of our launch promotional materials?

FDA Response:

No, we do not have any feedback to provide at this time regarding sharing assessments of biosimilarity with prescribing HCPs.

OPDP encourages Pfizer to submit draft promotional materials to OPDP for advisory comment prior to use. We refer Pfizer to the April 2015 Draft Guidance for Industry: Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertising Materials for Human Prescription Drugs. This guidance provides information on the content and format of submissions of promotional materials in

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

either electronic (eCTD) or hard-copy format. If you have any questions about using the eCTD pathway for promotional materials, please direct those questions to our dedicated eCTD team at this address: opdpectd@fda.hhs.gov.

For more information, you can also refer to the FDA website:
<http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm153574.htm>. This page contains links to guidances, presentations, and other helpful information on eCTD submission.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 8:

Pfizer understands that the BLA is being filed during BsUFA I, however, it is our understanding that the new user fee program, BsUFA II, would allow for additional communication between FDA review teams and biosimilar applicants in the form of mid-cycle communications and late-cycle meetings. Would the Agency be open to discussing issues and potentially grant meetings during review when warranted in light of not having planned mid and late cycle interactions?

FDA Response:

If your marketing application is received before October 1, 2017 your application will be reviewed according to the procedures and goals established under BsUFA I. However, if during the course of review we identify issues that warrant discussion, the Agency is willing to discuss issues and provide appropriate communications during the review cycle as appropriate and necessary.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 9:

The Agency has stated that it plans to hold only one Advisory Committee Meeting for each of the first new biosimilars for a reference product. Does the Agency have comments on the timing/likelihood of a potential Advisory Committee Meeting?

FDA Response:

The decision to hold an Oncologic Drugs Advisory Committee meeting for your product will be a review issue.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 10:

Does the Agency have any feedback on the 120-day safety update consisting of a single supplemental CSR for Study B3271002?

FDA Response:

Your proposal for the single supplemental CSR appears acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 11:

Does the Agency have any feedback regarding post-Week 53 data collected but not analyzed for patients prior to implementation of Protocol amendment 3 for Study B3271002?

FDA Response:

No.

Pfizer Reply:

Pfizer would like clarification that "No" means that the Agency agrees with Pfizer's proposal and has no concerns with the approach that data collected post-Week 53 for study B3271002 will not be analyzed or submitted as part of the submission including the supplemental CSR (with a data cut-off of January 2017).

Meeting Discussion:

The Agency agreed with Pfizer's proposal and had no concerns with this approach. If questions arise during review of your BLA that this data could address, the Agency may request that Pfizer submit this data to the BLA.

Question 12:

Does FDA have any feedback on the proposed organization of CTD Section 3.2.R.3 including cross references to other sections in Module 3, as shown in Appendix 1?

FDA Response:

The organization appears to be acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 13:

Does FDA have any feedback on the proposed presentation of summary information (Appendix 1) regarding the lots of PF-05280014 and trastuzumab- US/trastuzumab-EU used in the analytical biosimilarity assessment?

FDA Response:

Your proposed presentation of summary information regarding the analytical similarity assessment in Section 3.2.R.3 appears acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 14:

Does FDA have any feedback on the proposed presentation of results in CTD Section 3.2.R.3 (Appendix 1) including summary data tables?

FDA Response:

Your proposed presentation of results in Section 3.2.R.3 appears acceptable. The adequacy of the data to support an assessment of analytical similarity will be a review issue.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 15:

Does FDA have any feedback on the proposed locations for the analytical methods as proposed in Table 5?

FDA Response:

Your proposed locations for the analytical method descriptions appear acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 16:

Does FDA have any feedback on the inclusion of analytical method validation summaries for routine release test methods in CTD Section 3.2.S.4.3 or Section 3.2.P.5.3 and the characterization method qualification reports provided in CTD Section 3.2.R.3?

FDA Response:

Your proposed locations for analytical method validation summaries for routine test methods and characterization method qualification reports appear acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 17:

Does the FDA have any feedback on the proposal to reference the drug product manufacturing site's DMF for the facilities and equipment information?

FDA Response:

Your proposal to reference the manufacturing site's DMF for the facilities and equipment information appears acceptable.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 18:

In anticipation of the PAI of PF-05280014 drug product manufacturing activities at Pfizer Puurs approximately 2-5 months after the BLA submission, Pfizer is seeking to be allowed the flexibility to schedule the inspection of (b) (4) 440 mg drug product manufacturing. Could the Agency comment on this request?

FDA Response:

(b) (4)

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 19:

Will FDA expect to observe manufacture of the BWFI diluent as part of the PAI at Pfizer Puurs, (b) (4)

FDA Response:

(b) (4) filling lines should be in operation during the pre-license inspection of the DP manufacturing facility.

Pfizer Reply:

Pfizer acknowledges the Agency's response and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

Question 20:

Pfizer will make available for review the PF-05280014 raw data generated at the respective manufacturing sites and site subject matter experts during the manufacturing PAIs. For the review, if required, of the majority of the raw data supporting the demonstration of analytical similarity, generated at other testing sites, Pfizer is seeking a mechanism to facilitate the review and proposes to host the review at the Pfizer office in Silver Spring, MD. Does FDA have feedback on this proposal?

FDA Response:

FDA may inspect the testing sites at which testing to support analytical similarity was performed.

Pfizer Reply:

Pfizer acknowledges the Agency's comment. In the BLA, Pfizer will provide a list of testing sites that were involved in generating analytical similarity data. These sites will be available for FDA inspection. Meanwhile, Pfizer continues to offer the Silver Spring, MD site as a consolidated location for auditing at the Agency's discretion.

Meeting Discussion:

The Sponsor asked if the Agency would consider their Silver Spring, MD site as a consolidated location for auditing the analytical similarity data. The Agency informed the Sponsor all testing sites should be ready for inspection at the time of BLA submission.

Post meeting FDA Response:

The Pfizer site in Silver Spring, MD may be an acceptable location for review of the analytical similarity raw data; however, each analytical testing site may be subject to an

inspection. FDA will make an assessment of whether to conduct a pre-approval inspection of your analytical similarity testing sites during review of the BLA.

FDA Additional Comments:

Product Quality Microbiology Additional Comments:

We are providing additional product quality microbiology comments for you to consider for the preparation of your 351(k) BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:



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Product Quality Additional Comments:

Provide a listing of all sites where the analytical similarity assessment was conducted and identify the testing site(s) for each method. Report this information in the 3.2.R, Regional section of your BLA application.

Clinical Pharmacology Additional Comments:

- 1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the BLA:**
 - a. Include the rationale for the selected dose used in the PK study in the BLA (e.g., Module 2 Summary of Clinical Pharmacology document).**
 - b. Include an evaluation of the impact of immunogenicity on the activity, safety, and pharmacokinetics, as is applicable, for the studies included in the application.**
 - c. Submit all the PK bioanalytical methods and validation reports.**
 - d. Present the PK parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range, as appropriate.**
 - e. Include complete datasets for the PK studies. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.**
 - f. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

Pfizer Reply:

Pfizer acknowledges the Agency's Additional Comments and no additional discussion is required.

Meeting Discussion:

No discussion occurred.

3.0 OTHER

Pfizer Reply:

Pfizer acknowledges the Agency's Other Comments and no additional discussion is required.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care

Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to initiating your comparative clinical study (see additional comments below regarding expected review timelines).

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of

IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA and Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

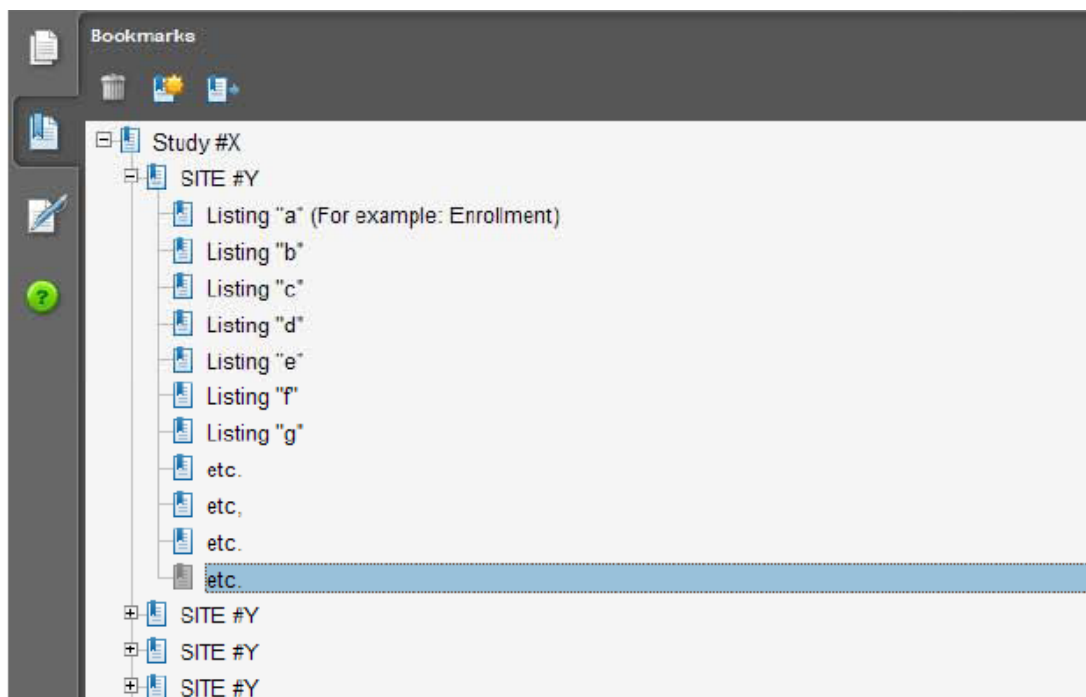
1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the 351(k) BLA for each of the completed clinical studies:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each clinical study: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the clinical studies)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each clinical study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for Items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The Item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the Item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

SAKAR M WAHBY
02/28/2017

LALEH AMIRI KORDESTANI
02/28/2017