

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761099Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 117038

**MEETING MINUTES**

Pfizer, Inc.  
Attention: Riddhi Dedhia  
Senior Manager, Worldwide Safety and Regulatory  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Dear Ms. Dedhia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06439535.

We also refer to the teleconference between representatives of your firm and the FDA on September 12, 2017. The purpose of the meeting was to discuss the overall content and format of the planned 351(k) Biologics License Application (BLA) submission for PF-06439535.

A copy of the official minutes of the teleconference 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 (301) 796-7910.

Sincerely,

*{See appended electronic signature page}*

Shubhangi (Gina) Mehta, PharmD  
Regulatory Health Project Manager  
Division of Oncology Products 2  
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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** Biosimilar Biological Product Development (BPD) Type 4  
**Meeting Date and Time:** September 12, 2017 11:00 AM to 12:00 PM  
**Meeting Location:** Teleconference  
**Application Number:** IND 117038  
**Product Name:** PF-06439535  
**Indication:** PF-06439535 is being developed for the same indications as approved for US-licensed Avastin  
**Sponsor/Applicant Name:** Pfizer, Inc.  
**Meeting Chair:** Martha Donoghue  
**Meeting Recorder:** Shubhangi (Gina) Mehta

**FDA ATTENDEES**

Patricia Keegan	Division Director
Martha Donoghue	Clinical Team Leader
Sandra Casak	Clinical Reviewer
Whitney Helms	Nonclinical Team Leader
Emily Wearne	Nonclinical Reviewer
Yan Wang	Product quality reviewer
Chana Fuchs	Product Quality Team Leader
Meiyu Shen	CMC Statistics Team Leader
Chao Wang	CMC Statistics Reviewer
Sarah Schrieber	Clinical Pharmacology Team Leader
Safaa Burns	Clinical Pharmacology Reviewer
Bo Chi	Microbiology Team Leader
Virginia Carroll	Microbiology Reviewer
Lisa Rodriguez	Statistics Team Leader
Uma Siangphoe	Statistics Reviewer
Navid Homayouni	Office of Scientific Investigations
Mike Shanks	Facilities Reviewer
Gina Mehta	Regulatory Project Manager
Anne Rowzee	TBBS/Science Policy Analyst
Sue Lim	TBBS/Team Lead

## **SPONSOR ATTENDEES**

Gregory Roberts	Biosimilar Development Asset Lead
Louise Dowling	CMC Regulatory Lead
Riddhi Dedhia	Global Regulatory Lead
Karen Rule	Analytical R&D Lead
Zhanna Jumadilova	Clinical Lead
Cheryl Li	Clinical Pharmacology Lead
Raheel Shafi	Safety Risk Lead
Fiona Hilton	Statistics Lead
Paul Brown	Global Supply
Robert Schaum	Regulatory lead

## **BACKGROUND**

### **Indication**

Pfizer will seek licensure of PF-06439535 for all currently approved indications for US-licensed Avastin in their planned 351(k) BLA. However, at the time of Pfizer's planned BLA submission, the US-licensed Avastin ovarian cancer indications will remain protected by orphan exclusivity and therefore FDA cannot license PF-06439535 for these indications until after exclusivity expiry.

### **Regulatory**

On July 12, 2017, Pfizer requested a BPD Type 4 meeting to discuss and obtain concurrence on the overall content and format of the planned 351(k) BLA submission for PF-06439535, as a proposed biosimilar to US-licensed Avastin. Specifically, Pfizer proposes to discuss the summary content and format of the 351(k) BLA, including Chemistry, Manufacturing, and Controls (CMC)/quality, nonclinical and clinical sections, the timelines for pre-license inspections and the proposed concept for labeling.

Pfizer is currently planning for the submission of its BLA under Section 351(k) of the Public Health Services Act in January 2018.

FDA sent Preliminary Comments to Pfizer on September 11, 2017.

### *Key Regulatory History:*

- May 22, 2013: Biosimilar Initial Advisory meeting held to obtain preliminary feedback on the CMC/quality, nonclinical and clinical development strategy for PF-06439535 as a proposed biosimilar to US-licensed Avastin.
- January 3, 2014: Submitted IND 117038 containing Protocol B7391001, entitled "Phase I, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced from US and EU Administered to Healthy Male Volunteers" for the development of PF-06439535. IND was allowed to proceed.
- February 19, 2014: FDA issued an Advice/Information letter with statistical and CMC comments and recommendations regarding Protocol B7391001.

- April 2, 2014: Pfizer submitted amendment #2 for Protocol B7391001. Changes included addition of an outpatient visit on Day 100 for the assessment of anti-drug antibodies (ADA) at lower, non-interfering drug concentrations.
- July 16, 2014: BPD Type 2 meeting held to discuss the study design, immunogenicity assessment strategy, and statistical approach for the proposed randomized clinical Study B7391003 intended to demonstrate no clinical differences between PF-06439535 when compared with EU-approved bevacizumab in combination with paclitaxel and carboplatin based on assessment of overall response rate at 19 weeks in patients with non-squamous non-small cell lung cancer (NSCLC), and Pfizer's responses to FDA's February 19, 2014 advice letter.
- April 15, 2015: BPD Type 3 meeting was held to discuss the data generated in the PF-06439535 development plan to date, including the comparative analytical characterization, and the clinical pharmacokinetic (PK) similarity assessment, as well as their proposed comparative clinical study in non-squamous NSCLC (Study B7391003).
- August 11, 2016: FDA issued an Agreed Initial Pediatric Study Plan-Agreement letter acknowledging Pfizer's intention to request a full waiver of the requirement to assess the safety and effectiveness of PF-06439535 in pediatric patients for each of the indications approved for US-licensed Avastin for which Pfizer intends to seek licensure.
- February 13, 2017: BPD Type 2 teleconference meeting was held between Pfizer and FDA, to discuss specific CMC (protein concentration tier and stability data) and clinical (B7391003 data availability) issues as well as broad questions about the format and content for the planned BLA.
- June 8, 2017: Pfizer submitted request for review of proposed proprietary name  
(b) (4)

### **Chemistry, Manufacturing, and Controls**

PF-06439535 is being developed in the same strengths and presentation as US-licensed Avastin but in a different formulation. Pfizer's analytical development program for PF-06439535 has been discussed through numerous communications, and included presentation of analytical similarity data for PF-06439535 that includes analyses of higher order structure, biological function, product- and process-related impurities, and degradation profiles in comparison to US-licensed Avastin and EU-approved bevacizumab. Analytical data has also been included to support the scientific bridge to justify the relevance of clinical data generated with EU-approved bevacizumab in support of a demonstration of no clinically meaningful differences between PF-06439535 and US-licensed Avastin.

Pfizer plans to submit in the BLA comparative physicochemical and functional characterization as well as the comparative degradation studies of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab, which have been stated to include results from 46 US-licensed Avastin drug product (DP) lots (400 and 100 mg strengths), 49 EU-approved bevacizumab drug product lots (400 and 100 mg strengths), 10 PF-06439535 drug substance (DS) batches and 16 PF-06439535 drug product lots (8 lots of PF-06439535 100 mg and 8 lots of PF-06439535 400 mg) manufactured at the commercial scale at the commercial facility, as well as 2 PF-06439535 development scale drug substance batches ( (b) (4) scale).

## Nonclinical

Pfizer's in vitro nonclinical program for PF-06439535 includes pharmacology studies comparing the functional and binding properties of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab. Pfizer's in vivo nonclinical program includes a 1-month repeat-dose toxicology study in sexually and skeletally immature male cynomolgus monkeys comparing PF-06439535 and EU-approved bevacizumab, and a 2-week repeat-dose non-comparative toxicology study in Sprague-Dawley rats with PF-06439535. No additional nonclinical studies are planned.

## Clinical

Pfizer's clinical development program includes the following studies:

- **Study B7391002**, a completed single-dose pilot pharmacokinetic (PK) study of EU-approved bevacizumab to assess the inter-subject variability in PK of bevacizumab in healthy subjects.
- **Study B7391001**, a three-arm study to assess both PK similarity between PF-06439535 and US-licensed Avastin, and to establish the scientific bridge to justify the relevance of data obtained from use of EU-approved bevacizumab in the comparative clinical study, Study B7391003. The bridge was established through 3 pairwise comparisons between PF-06439535 and US-licensed Avastin, PF-06439535 and EU-approved bevacizumab, and between US licensed-Avastin and EU-approved bevacizumab. Among 101 subjects who received a single 5 mg/kg dose of one of the three products, 97 subjects had a sufficient number of PK samples to be included in the PK analysis population. Based on the summary results provided, PK similarity appears to have been demonstrated for all 3 pairwise comparisons as the 90% confidence intervals for the test-to-reference ratios of  $C_{max}$ ,  $AUC_T$ , and  $AUC_{0-\infty}$  were all within the pre-specified margin of 80% to 125%.
- **Study B7391003**, a comparative clinical study intended to demonstrate that there are no differences in the clinical outcomes, PK, and immunogenicity profile of PF-06439535 as compared to EU-approved bevacizumab in patients with advanced non-squamous NSCLC. Patients with unresectable or metastatic non-squamous NSCLC were randomized (1:1) to receive to receive 4-6 cycles of either 15 mg/kg PF-06439535 or 15 mg/kg EU-approved bevacizumab plus carboplatin/paclitaxel, followed by monotherapy with the assigned blinded PF-06439535 or EU-approved bevacizumab. Randomization was stratified by region, sex, and smoking history (never/ever). The meeting package includes the top-line results for the primary endpoint based on all available tumor assessment data as of the cutoff date of May 8, 2017 (20% of active patients are still in long term follow up at Week 55).

A total of 719 patients were randomized (358 and 361 patients to the PF-06439535 and EU-approved bevacizumab arms, respectively) and all but 5 patients received treatment. At the time of data cut-off, 341 (47.4%) patients had discontinued the study and 373 (51.9%) were ongoing (184 patients had discontinued treatment and are in long-term follow-up). Rates of treatment discontinuation were 72.9% and 72.6% for PF-06439535 and EU-approved bevacizumab, respectively. Pfizer states that demographics at baseline were comparable between the two treatment arms. Pfizer states that the study met its primary endpoint. The ORR was 45.3% (95% CI 40.0, 50.7) in the PF-06439535 arm and 44.6% (95% CI 39.4, 49.8) in the EU-approved bevacizumab arm, with a risk ratio of ORR of

1.0146 (90% CI 0.88, 1.16). Pfizer states that there were no statistically significant differences in the secondary endpoints of duration of response, PFS and OS. The submission contains tables with summaries of adverse events, and the incidence of post-treatment ADAs was very low (0.6% in each arm).

## SPONSOR QUESTIONS AND FDA RESPONSES

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).

1. *Please refer to background on page 20 of the meeting package.*

**Does the FDA have any feedback on the proposed structure and format of the PF-06439535 351(k) BLA as presented in Appendix 5 of the Meeting Package Materials such that it meets the FDA's expectations for e-CTD submission?**

**FDA Response:** FDA has the following comments regarding the proposed structure and format of the planned 351(k) BLA submission:

- a. The proposed structure and format of the quality sections generally appear to be adequate to support the filing of a 351(k) BLA. However, the proposed content of the BLA does not appear to be acceptable. The following comments, and those discussed in the FDA responses to Questions 7, 8, 9, 10, 11, 12, and FDA Additional Comments 14 through 16 should be addressed.
  - i. U.S.-licensed Avastin is licensed in 2 strengths, a 100 mg/4mL vial and a 400 mg/16mL vial. In order to ensure efficient review, FDA requests that within the relevant 3.2.P.X modules, there should be individual documents for each of these strengths, as relevant to the particular section.
  - ii. Executed DP batch records for both 100 mg/4mL and 400 mg/16mL vial formats should be included in the BLA.
  - iii. The summary validation data and information related to sterility assurance of the drug product should be included within the appropriate sections of Module 3 (e.g., P.3.5) rather than in the Drug Master File (DMF) as proposed, to facilitate the review of the product specific supporting information.
  - iv. The in-use compatibility study results of the drug product with various infusion sets should be submitted to the BLA in Section 3.2.P.2.
- b. The proposed structure and format of the nonclinical pharmacology/toxicology sections generally appear to be adequate to support the filing of a BLA.
- c. The proposed structure and format of the clinical pharmacology sections generally appear to be adequate to support the filing of a BLA. Regarding adequacy of the clinical pharmacology content of the BLA, FDA reminds Pfizer to include

information and datasets as requested in the Additional Clinical Pharmacology Comment 9a through 9f from the February 13, 2017, BPD Type 2 meeting minutes.

- d. The proposed structure and format of the clinical sections generally appear to be adequate to support the filing of a BLA. However, as discussed in the February 13, 2017, BPD Type 2 meeting regarding the datasets for Study B7391003, the following should be addressed.
  - i. Provide all raw data and derived variables in .xpt format. FDA strongly recommends submission of datasets using CDISC standards.
  - ii. Provide SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
  - iii. Provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert as well as any interim analysis if performed.
  - iv. Provide a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should also be included.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

2. *Please refer to background on page 21 of the meeting package.*

**Does FDA 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 6 in CTD Section 1.12.11 such that it meets the FDA's expectation for a user-friendly navigation tool to the requisite data within the BLA to support compliance with 351(k) statutory requirements?**

**FDA Response:** FDA has no objections to the proposed approach for the "351(k) roadmap".

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

3. *Please refer to regulatory background on page 20 of the meeting package.*

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

**FDA Response:** Refer to the comments listed in the FDA responses to Questions 1 and 12 for advice on the proposed structure of the BLA.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

4. *Please see background on page 21 of meeting package referencing ISS and ISE.*

**During the PF-06439535 biological product development Type 2 (BPD2) meeting held on 13-Feb-2017 (FDA meeting minutes [Appendix 3]), FDA agreed Pfizer's proposal of M 5.3.5.3 (Integrated Summary of Efficacy [ISE]/Integrated Summary of Safety [ISS]) to be a mapping document, however, advised to revisit this approach at the BPD4 meeting. See below background and mock-up of Module 5.3.5.3 (Figure 2 for ISE and Figure 3 for ISS). This mock-up is provided as an exemplary of the formatting and layout only. The specific headings and content will be amended for the BLA submission. Pfizer would like to re-affirm FDA's acceptance of M5.3.5.3 as a mapping document in the PF-064359535 351(k) BLA?**

**FDA Response:** FDA agrees with the proposed structure of the ISE and ISS which is consistent with the agreements reached during the meeting of February 13, 2017. Also, please refer to FDA's response to Question 1 regarding a mock-up define file.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

5. *Please see background for this question on page 25 and 26 of meeting package referencing Proposed Labeling Concept.*

*In accordance with the draft guidance for "Labeling for Biosimilar Products, March 2016", Pfizer is generating its PF-06439535 (bevacizumab-xxxx) biosimilar product labeling. The label will be similar to the FDA-approved reference product (Avastin) labeling and the product identification in each of the sections will depend on the information being described. Some differences from Avastin US package insert (USPI) will be the company name, address, product (proprietary/non-proprietary) name, National Drug Code (NDC) number, revision date and the inclusion of a biosimilar statement. As required under 21 CFR201.56(c)(1), PF-06439535 (bevacizumab-xxxx) product labeling will meet the content and format requirements of the Physician Labeling Rule (PLR) and Pregnancy and Lactation Final Labeling Rule (PLLR). Pfizer's proposed approach to the labeling content is provided in Table 5. Since the proprietary name of PF-06439535 is currently under FDA review, herein the table, "TRADENAME" will be referred to as the proprietary and "bevacizumab-xxxx" as the non-proprietary name of PF-06439535.*

**Does FDA have any feedback with the proposed labeling concept for PF-06439535 to support the BLA submission?**

**FDA Response:** At the time of Pfizer's planned BLA submission, the US-licensed Avastin ovarian cancer indications will remain protected by orphan exclusivity and therefore FDA cannot license PF-06439535 for these indications until after exclusivity expiry. Therefore, information related to this indication should be removed from relevant sections (e.g., Highlights, Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, and Clinical Studies) of the proposed PF-06439535 label.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

6. *Pfizer is currently planning for submission of its PF-06439535 BLA under the 351(k) pathway in January 2018 and in light of the BSUFA II implementation from 01-Oct-2017, Pfizer understands that FDA will be applying the model "The Program" to review our 351(k) submission. In that regard, Pfizer proposes to submit a complete application in the original 351(k) submission (see Appendix 5 TOC) and do not anticipate submitting any minor components within 30 days after our original submission. Also, Pfizer strongly supports the timing and nature of interactions and information exchange that will occur as part of "The Program," and do not foresee a need to create an alternative approach in the form of a Formal Communication Plan.*

**Does FDA agree with our proposal and have any feedback?**

**FDA Response:** Yes, FDA agrees with the proposal to submit a complete application in the original 351(k) submission and does not have additional feedback at this time.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

7. *The proposed outline for the organization of CTD Section 3.2.R.3 Comparative Physicochemical and Functional Assessment for the PF-06439535 351(k) BLA is provided in Appendix 4. Pfizer may make minor adjustments to this format prior to submission of the 351(k) BLA but anticipates that the overall organization described in Appendix 4 will remain the same.*

*This is the fifth BPD4 engagement within the Pfizer/Hospira proposed biosimilar portfolio that the Sponsor has had with the FDA. The proposed format for PF-06439535 presented in Appendix 4 has been informed by the previous discussions. (questions 7-9)*

**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 4?**

**FDA Response:** For ease of review, it would be useful if each structural group, e.g. primary structure, higher order structure, product related substances/impurities, biological activity, etc. would be in its own document as a leaf in the 3.2.R.3 Comparative Physiochemical and Functional Assessment (i.e. the analytical similarity assessment) tab. In section 3.2.R.3 include the listing of all sites used for assessment of analytical similarity and specify the activities performed at each site.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

8. **Does FDA have any feedback on the proposed presentation of summary information (Appendix 4) regarding the lots of PF-06439535/bevacizumab-US/bevacizumab-EU used in the analytical biosimilarity assessment?**

**FDA Response:** Please provide detailed information for all the batches/lots of PF-06439535 manufactured, including those used in the analytical similarity assessment. This information should include, at a minimum, batch/lot number, date of manufacture, manufacturing site, manufacturing process (e.g., manufactured by the commercial process, small scale etc.) and use (e.g., comparative characterization, comparative force degradation study etc.). For drug substance (DS) lots, include identification of the subsequent DP lots manufactured from each of the DS lots. For DP lots, include information on DP strength, the DS lots used to source each of the DP lots, and the use of each DP lot (e.g., the toxicology or clinical studies in which the lot was used, lots to be marketed, etc.).

**Pfizer's September 11, 2017, email response:** The sponsor will include detailed information for all batches and lots of PF-06439535 manufactured, in 3.2.S.4.4/3.2.P.5.4 Batch Analyses, and lot genealogy information in 3.2.P.2.3/3.2.R.3. All the information requested by the FDA (e.g. batch/lot number, date of manufacture etc.) is provided in tabular format in these sections. We propose to include a table in 3.2.R Similarity with hyperlinks to these sections.

***Would that be adequate to support the Agency's request?***

**Discussion at September 12, 2017 Teleconference:** FDA agreed to the proposal outlined in Pfizer's September 11, 2017 response.

9. **Does FDA have any feedback on the proposed presentation of results in CTD Section 3.2.R.3 (Appendix 4) including summary data tables?**

**FDA Response:** In addition to the tabular listing of individual data from each lot of PF-06439535, US-licensed Avastin and EU-approved bevacizumab, please present each quality attribute in figures to enable a visual comparison of the results both within the specific comparator group (US-licensed Avastin, PF-06439535, and EU-approved bevacizumab) and across the three groups. FDA has found that identification of each comparator group by a specific color helps in the analysis of the data when multiple lots of each group are analyzed side by side.

FDA recommends that Pfizer provide electropherogram or chromatogram data for the applicable assays of batches/lots of PF-06439535, US-licensed Avastin and EU-approved bevacizumab used for assessment of analytical similarity.

Section 3.2.R.3.5-Appendix is identified as including the full data from 46 US-licensed Avastin, 49 EU-approved bevacizumab, and 28 PF-06439535 (12 DS (including 1 reference material), 16 DP batches/lots). The section should clearly identify independent lots of PF-06439535 (i.e. lots that are not derived from the same drug substance lot).

For quality attributes evaluated using Tier 1 testing, specify the statistical equivalence test used in Section 3.2.R.3.1.1. As the numbers of lots for US-licensed Avastin, EU-approved bevacizumab, and PF-06439535 stated in Section 3.2.R.3.5-Appendix are highly unbalanced, provide detailed information on how the sample size imbalance is taken into account in the statistical equivalence test. Also provide selection criteria and justification if subsets of the available drug lots are used in the Tier 1 quality attribute assessment. Please refer to Additional CMC Comments.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

10. *The analytical methods used for testing of PF-06439535 generally fall into two categories: (1) those used for routine and formal stability testing, validated per ICH Q2 (R1), and (2) those used for additional characterization, qualified to confirm the suitability of the analytical assays used in the analytical similarity assessment using relevant validation parameters outlined in ICH Q2(R1). The analytical methods for routine in-process testing, release and stability testing represent a subset of the overall physicochemical and functional methods used to support product characterization. Additional characterization methods were developed and implemented to support a comprehensive characterization of PF-06439535 and comparative testing of PF-06439535 with bevacizumab-US and bevacizumab-EU. Analytical method summaries for the characterization methods used to support the analytical biosimilarity assessment will be provided in CTD Section 3.2.R.3. The inclusion of the characterization methods in Section 3.2.R.3 will enable reviewers to readily access the method summaries during*

*evaluation of the comparative biosimilarity data. The proposed location for the analytical method descriptions for inclusion in the 351(k) BLA is shown in Table 6 (page 29 of meeting package). Cross-references to analytical method descriptions will be provided in the CTD sections that describe the testing and/or control strategies associated with the specific analytical methods.(questions 10-11)*

**Does the FDA have any feedback on the document proposed locations for the analytical methods as proposed in Appendix 4?**

**FDA Response:** The proposed locations for the analytical method descriptions appear acceptable. Please include the full protocol for each analytical method in the relevant eCTD Sections.

**Pfizer's September 11, 2017, email response:** The sponsor will include extensive descriptions of method procedures for release methods in 3.2.S.4.2 and 3.2.P.5.2. Many of these methods are also used in the similarity assessment. Additional characterization methods for the biological activity used in the similarity assessment will have detailed technical reports supplied in 3.2.R.3. These reports include detailed method summaries. Within 3.2.R.3, we supply a table outlining the location of each method's detail.

*Is this information adequate to support the Agency's request?*

**Discussion at September 12, 2017 Teleconference:** FDA agreed to the proposal outlined in the September 11, 2017 response. Pfizer agreed to provide the SOPs for each method described in 3.2.S.4.2 and 3.2.P.5.2 and to provide either the SOP or a detailed description of the assay methodology for all methods described in 3.2.R.3.

11. **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?**

**FDA Response:** Submission of analytical method validation summaries in eCTD Section 3.2.S.4.3 or Section 3.2.P.5.3 is appropriate. In addition to the method validation summaries described, the BLA should also include the full method validation reports for all assays used for release and stability of the drug substance and drug product. For assays that may be executed in process after specific manufacturing steps in lieu of release testing (e.g. host cell protein assay, DNA, etc.), the assay validation reports should also be included in the BLA.

To assist in the BLA review, as part of the summary, please include tables with active links to all the validation reports, qualification reports, method transfer reports and the method protocols.

Method validation or qualification reports should also be included in the BLA for those methods used in the analytical similarity assessment in addition to summarized information.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

12. *PF-06439535 drug substance is manufactured at Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., at Andover, MA 01810, USA (Pfizer, Andover) and the PF-06439535 drug product is manufactured at Pharmacia & Upjohn Company, a subsidiary of Pfizer Inc., at Kalamazoo, MI 49001, USA (Pfizer, Kalamazoo) For the PF-06439535 drug substance manufacturing site, Pfizer Andover, Pfizer will provide facilities and equipment information including manufacturing flow, information on the developmental or approved products manufactured or manipulated in the same areas and measures taken to prevent cross contamination in 3.2.A.1 Facilities and Equipment section. For the PF-06439535 drug product manufacturing site, Pfizer, Kalamazoo, the 3.2.A.1 Facilities, and Equipment section will cross-reference the Pfizer Kalamazoo Type V Drug Master File (DMF) # (b) (4) The DMF will contain detailed information related to (b) (4) The DMF provides the level of information aligned with FDA's expectations for a sterile manufacturing facility and will contain all appropriate product- specific information at the time of BLA submission. The DMF will be updated as needed and kept current. DMF updates relevant to PF-06439535 will be filed to the PF-06439535 BLA either via BLA supplement (as appropriate) or via the BLA annual report.*

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

**FDA Response:** FDA does not agree with the proposal to reference the drug product manufacturing site's DMFs for product-specific information supporting the manufacturing process and control described in Sections 3.2.P.3.3. and 3.2.P.3.4. Detailed information related to (b) (4)

should be contained within Section 3.2.P.3.5 *Process Validation and/or Evaluation* of the BLA. See the Additional Comments section for product quality microbiology information expected for a complete BLA submission.

FDA notes that Pfizer only included a letter of authorization (LOA) for Kalamazoo Type V DMF (b) (4). In the BLA, please include LOAs for all relevant Master Files, for example, master files for the container closure components. In the LOA, provide the exact location of the data being referenced by date of submission, volume, and page numbers as appropriate.

**Pfizer's September 11, 2017, email response:** Pfizer's established approach to drug product facility DMFs includes to reference the drug product manufacturing site's DMF for product-specific information supporting the manufacturing process and control described in Sections 3.2.P.3.3. and 3.2.P.3.4. and to maintain the DMF and BLA

throughout the product lifecycle. Previous engagements with the Agency support this approach.

Reference: FDA meeting minutes from IND 114828 PF-06438179 Infliximab-Pfizer BPD Type 4 meeting on Nov 22, 2016, question 9 Page 8: “Referencing drug product facility DMFs (b) (4) validation data is not sufficient if the information in the DMF is not product-specific .....Additionally, sections 3.2.P.3.3 and 3.2.P.3.4 of the application should include sufficient detail regarding the PF-06438179 manufacturing process and process controls as discussed under the additional product quality microbiology comments. All information for facilities and equipment should be current in the DMF when the application is submitted.”

Referencing the DMF in Question 12, allows the Sponsor to avoid replication of information being submitted and reviewed by the Agency, and avoids that duplication persisting throughout the lifecycle of the product. The Sponsor would appreciate the opportunity to discuss the Agency’s request further.

**Discussion During September 12, 2017 Teleconference:** FDA acknowledges comments captured in previous meeting minutes, however, based on recent experience and current thinking, this advice has changed. Specifically, FDA has experienced challenges in finding the relevant information in cross-referenced DMFs that contain information pertaining to multiple products and has had difficulty tracking changes in DMFs over the BLA life cycle. FDA stated that all relevant information and data needed for review of the BLA, including that related to (b) (4) product must be provided. For the reasons cited above, FDA strongly recommends that all information be included in the BLA, however, as an alternative, FDA agreed that product specific information may be cross referenced to a DMF if the location of the information is clearly identified.

In response to FDA’s request for clarification regarding how product specific changes (i.e., changes specific to PF-06439535) made to DMFs will be tracked over the BLA life cycle, Pfizer stated that such changes will be identified in the annual report to the BLA. FDA asked Pfizer to further clarify whether a manufacturing change proposed by the DMF holder that could potentially affect product quality will be submitted as a supplement to the BLA under the appropriate reporting category. Pfizer confirmed they would submit a supplement to the BLA for DMF changes that could affect product quality. FDA stated that this strategy is acceptable.

13. *Please see reference to Pre-approval inspection on page 30 of the meeting package, 10.2.4. regarding table for tentative manufacturing schedule.*

*Pfizer anticipates FDA may conduct pre-approval inspections (PAIs) to review the manufacturing activities. All manufacturing facilities listed in 3.2.S.2.1 and 3.2.P.3.1 will be ready for inspection at the time of BLA submission in accordance with 21 CFR 600.21*

*and 601.20(b)(2). We will include in Module 1 of the 351(k) BLA under section 1.3, a complete list of manufacturing and testing sites with their corresponding FEI numbers, and manufacturing schedule for the drug substance and drug product manufacturing sites.*

**Does the FDA have comments on the tentative manufacturing schedule for PAIs as presented here?**

**FDA Response:** Pfizer's proposal for the tentative Drug Product and Drug Substance manufacturing schedules for PLIs are acceptable provided the current plan for submission of Pfizer's 351(k) BLA in January 2018 does not change.

**Pfizer's September 11, 2017, email response:** Pfizer acknowledges Agency's comment. No further discussion is required.

**Discussion at September 12, 2017 Teleconference:** No discussion occurred

## **ADDITIONAL COMMENTS**

Refer to the below additional product quality microbiology comments for consideration, during development of the commercial manufacturing process and preparation of the 351(k) BLA submission:

14. All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.
15. The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:
  - a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
  - b. Bioburden and endotoxin data obtained during manufacture of three process qualification lots (3.2.S.2.5).
  - c. Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum

allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- d. Chromatography resin and UF/DF membrane lifetime study protocols and bioburden and endotoxin acceptance criteria for resins and membranes after sanitization. In addition, during the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization. Provide the bioburden and endotoxin acceptance criteria for resin and membrane storage validation (3.2.S.2.5).
  - e. Information and summary results from the shipping validation studies (3.2.S.2.5).
  - f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).
  - g. Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).
16. The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the FDA Guidance for Industry, entitled "*Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*," available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.
- a. Provide the following information in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.
    - i. Identification of the manufacturing areas and fill line, including area classifications.
    - ii. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.).
    - iii. Sterilizing filtration parameters, as validated by the microbial retention study.
    - iv. The wetting agent used for post-use integrity testing of the sterilizing filter and the acceptance criterion for post-use integrity testing.
    - v. Parameters for filling, stoppering and capping.
    - vi. Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product.
    - vii. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
    - viii. Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

- b. Provide the following information and validation data summaries in Section 3.2.P.3.5:
  - i. Bacterial filter retention study for the sterilizing filter.
  - ii. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the requalification program.
  - iii. In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
  - iv. Isolator decontamination summary data and information, if applicable.
  - v. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
  - vi. Shipping validation studies.
    - i. Capping validation demonstrating maintenance of container closure integrity.
- c. Provide the following information regarding drug product testing:
  - i. Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress ( $\leq 20$  microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.
  - ii. Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.
  - iii. Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time.
    - i. Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution and dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations which would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP

<51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours.

Refer to the below additional statistical comments for consideration, during development of the commercial manufacturing process and preparation of the 351(k) BLA submission.

17. FDA currently recommends that you use a step-wise approach to the evaluation of analytical similarity. The first step is a determination of the quality attributes that characterize the reference product in terms of its structural/physicochemical and functional attributes. In the second step, these quality attributes are then ranked according to their risk in terms of potential clinical impact on activity, PK/PD, safety, and immunogenicity. If there is limited understanding of the potential clinical impact of an attribute, then the attribute should be ranked with higher risk based on this uncertainty. Third, these attributes/assays are evaluated according to one of three tiers of statistical approaches based on a consideration of risk ranking as well as other factors as described below. FDA recommends that you provide a plan for demonstrating analytical similarity to the Agency as early as possible in your biosimilar development program, so that FDA may provide feedback on which attributes should be evaluated, the risk ranking of attributes, assignment of attributes into tiers for evaluation, and a statistical analysis plan for each tier.

FDA currently defines three tiers of evaluation corresponding to the use of three different methods for comparison of attributes. The use of these three tiers with appropriate similarity acceptance criteria is intended to support a demonstration that the proposed biosimilar is highly similar to the reference product. Equivalence testing (Tier 1) is typically recommended for quality attributes with the highest risk ranking and will generally include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. It is important to note, however, that there may be quality attributes categorized with the highest risk ranking that do not directly assess mechanism(s) of action, and are appropriate to evaluate in either of the remaining tiers. The use of quality ranges (Tier 2) is recommended for assessing quality attributes with a range of risk ranking criticality (from high to low), for which quantitative data can be obtained. An approach that uses raw data/graphical comparisons (Tier 3) is recommended for quality attributes with the lowest risk ranking or those quality attributes that are important but not amenable to formal tests of hypotheses or quantitative evaluation.

Other factors should be considered in assigning quality attributes and assays to a particular tier. These factors include, but are not limited to, the levels of an attribute in both the reference product and proposed biosimilar product (as determined by your testing), the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute. Based on these considerations, a quality attribute may be assigned to a tier different from that assigned based on risk ranking only.

Applicable data and cited literature should be provided to support risk ranking and the use of any additional factors in determining the appropriate tier of statistical assessment.

FDA also recommends that you carefully assess your analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that PF-06439535 is highly similar to the reference product, US-licensed Avastin. This could include, for example, considering the age of PF-06439535 and reference product lots tested, optimizing assays and pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate. The plan should specify the availability of proposed biosimilar and reference product lots for evaluation of each attribute and should include a rationale as to why the proposed number of lots is sufficient for evaluation of each attribute. The final analytical similarity report should be available when a 351(k) biologics license application is submitted.

You may propose an alternative statistical approach to evaluate quality attributes, in which case we encourage you to submit your proposal and request a meeting to discuss the approach with FDA prior to implementing your plan.

Further, we note that while a statistical approach to evaluate quality attributes of a proposed biosimilar product may be considered in support of a demonstration that the proposed biosimilar product is highly similar to the reference product, FDA's determination that a proposed biosimilar product is highly similar to the reference product will be based upon the totality of the evidence relevant to the assessment.

A potential approach for the different statistical tiers is described below:

- I. Tier 1 (Equivalence Test): To assess the equivalence in means, the null and alternative hypotheses are given by:

$$H_0 : \mu_B - \mu_R \leq -\delta \text{ or } \mu_B - \mu_R \geq \delta$$
$$H_a : -\delta < \mu_B - \mu_R < \delta$$

where  $\mu_B$  and  $\mu_R$  are the mean responses of the proposed biosimilar and reference product lots, respectively, and  $\delta > 0$  is the equivalence margin. A test of the equivalence hypothesis can be conducted by requiring the simultaneous rejection of the following two one-sided null hypotheses:

$$H_{01} : \mu_B - \mu_R \leq -\delta \text{ vs. } H_{a1} : \mu_B - \mu_R > -\delta$$
$$H_{02} : \mu_B - \mu_R \geq \delta \text{ vs. } H_{a2} : \mu_B - \mu_R < \delta$$

Acceptance Criterion: Equivalence in means would be accepted for the quality attribute if the  $(1-2\alpha)$  100% two-sided confidence interval of the mean difference is within  $(-\delta, \delta)$ .

- II. Tier 2 (Quality Range Approach): The quality range for a specific quality attribute is defined by the reference product data as  $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$ , where  $\hat{\mu}_R$  is the sample mean, and  $\hat{\sigma}_R$  is the sample standard deviation based on the reference product lots. The standard deviation multiplier ( $X$ ) should be scientifically justified for that attribute.

Acceptance Criterion: The statistical analysis would generally support analytical similarity for the quality attribute if a sufficient percentage of test lot values (e.g., 90 percent) fall within the quality range. The lots used for Tier 2 testing should, to the extent possible, be the same as those used for Tier 1.

- III. Attributes evaluated in Tier 3 correspond to those of lowest risk or are important but not amenable to formal tests of hypotheses or quantitative evaluation. Various forms of visual displays may be appropriate to compare the distribution of values from the biosimilar and reference lots, and subjective determination of the similarity is made based on those displays.

Additional considerations:

- a. Each lot should contribute one value for each attribute being assessed. Lot values are typically computed as the average of the replicates within each lot.
- b. FDA also recommends that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot.
- c. To the extent possible, the same lots should be used for Tier 1, Tier 2, and Tier 3 analysis. The lots used for Tier 3 analysis may be a subset of the lots used in Tier 1 and Tier 2 testing.
- d. High assay variability should not be a justification for a large  $\sigma_R$ . In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.
- e. In cases where the equivalence margins or quality ranges are too wide or too narrow, it may be scientifically justified and appropriate to revise the margins or range.

Additional recommendations for the Equivalence Test (Tier 1):

One potential statistical approach to evaluate Tier 1 quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g.,  $c \times \sigma_R$ ). The constant  $c$  would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, we selected  $\delta = 1.5 \sigma_R$  for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90% confidence

interval about the difference in sample means lies within  $(-1.5 \sigma_R, 1.5 \sigma_R)$ . If there were 10 biosimilar and 10 reference product lots, this test would have adequate power (e.g., at least 85%) to reject the null hypothesis in favor of equivalence when the true underlying mean difference between the proposed biosimilar and reference product lots is small, namely, equal to  $\sigma_R/8$ , assuming a test with  $\alpha = 0.05$ . If the true difference between products is less than  $\sigma_R/8$ , power will be increased.

Note that with this potential approach, the margin would be a function of the reference product variability; therefore, a larger margin would be used for attributes with larger variability. In addition, the confidence level would depend on the number of lots available for testing. For a more limited number of lots, one could consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy. In contrast, when a moderate or greater number of lots are available for testing, the equivalence test would be based on a 90% confidence interval.

In practice,  $\sigma_R$  in the proposed margin is usually not known and should be estimated from the reference product lots available to the biosimilar sponsor. With a limited number of lots, all reference product lots can be used to compute the confidence interval and to estimate the equivalence margin. In general, we also recommend a similar number of lots for both the proposed biosimilar and the reference products. When the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50 % larger), we recommend the following sample size imbalance adjustment to calculate the confidence interval of the mean difference:

$$(\hat{\mu}_B - \hat{\mu}_R) \pm t_{1-\alpha, df^*} \sqrt{\hat{\sigma}_B^2/n_B + \hat{\sigma}_R^2/n_R^*}$$

where  $n_R^* = \min(1.5 \times n_B, n_R)$ ,  $n_B$  and  $n_R$  are respectively the number of the proposed biosimilar lots and the number of the reference product lots;  $\hat{\mu}_B$  and  $\hat{\mu}_R$  are respectively the sample mean of the proposed biosimilar lots and the sample mean of the reference product lots;  $\hat{\sigma}_B^2$  and  $\hat{\sigma}_R^2$  are respectively the sample variance estimated by all the biosimilar lots and the sample variance estimated by all the reference lots;  $t_{1-\alpha, df^*}$  is  $1-\alpha$  quantile of the  $t$ -distribution with degrees of freedom  $df^*$  where  $df^*$  can be approximated by the Satterthwaite method. If the number of biosimilar lots,  $n_B$ , is 50% more than the number of reference lots,  $n_R$ , a similar approach can be applied with  $n_B^* = \min(1.5 \times n_R, n_B)$  for the confidence interval calculation.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed and agreed to as summarized in the minutes for the September 12, 2017 meeting.

- Pfizer confirmed that the application will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the BLA. Pfizer also confirmed that this information will be provided for the clinical pharmacology studies and bioanalytical testing sites (PK and immunogenicity).
- A preliminary discussion regarding the approach to developing the content for a REMS was held. FDA stated that a REMS would not be required for filing of this application, however, a final determination of the need for a REMS would be made during review of the application.
- Major components of the application will be submitted with the original application and are not subject to agreement for late submission based on Pfizer's intent to submit a complete application. Therefore, there are no agreements for late submission of application components.

### **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(1) 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.

We refer to your amendment dated February 24, 2016, which contained your initial Pediatric Study Plan (iPSP) and to your amendment dated July 13, 2016, which contained an Agreed Initial Pediatric Study Plan (iPSP) submitted in response to our letter of May 24, 2016. We confirmed our agreement to your July 13, 2016, Agreed iPSP, in our August 11, 2016, letter. This fulfills your requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of the 351(k) BLA submission.

## **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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- 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.
- 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

## **NONPROPRIETARY NAME**

On January 13, 2017, FDA issued a final guidance for industry entitled *Nonproprietary Naming of Biological Products*, available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm459987.pdf>, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor’s related analysis of proposed suffixes, which are considered a

“collection of information” under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA’s current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

### **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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>.

### **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), applicants must establish secure email. To establish secure email with FDA, send an email request to [SecureEmail@fda.hhs.gov](mailto: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).

### **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).

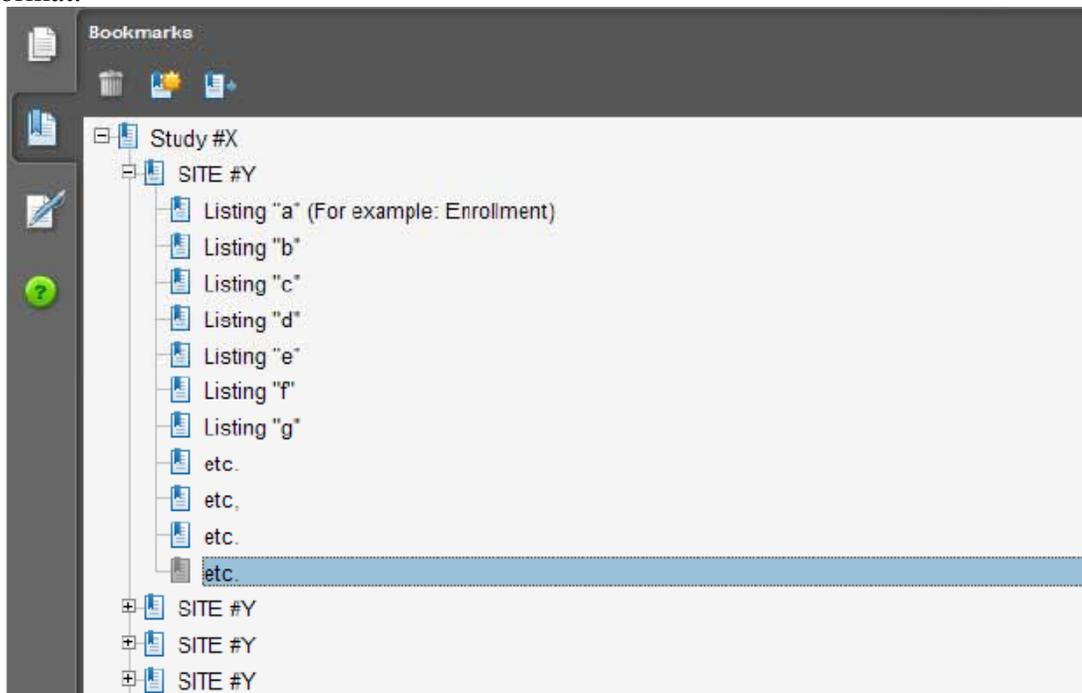
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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 <sup>1</sup>	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.

<sup>1</sup> 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](mailto:ESUB@fda.hhs.gov)

**ISSUES REQUIRING FURTHER DISCUSSION**

N/A

**ACTION ITEMS**

N/A

**ATTACHMENTS AND HANDOUTS**

N/A

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHUBHANGI H MEHTA  
10/03/2017



IND 117038

**MEETING MINUTES**

Pfizer Inc.  
Attention: Riddhi Dedhia  
Senior Manager, Worldwide Safety and Regulatory  
235 E. 42nd Street  
New York, NY 10017

Dear Ms. Dedhia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06439535.

We also refer to the teleconference between representatives of your firm and the FDA on February 13, 2017. The purpose of the meeting was to discuss questions regarding the CMC/stability data, clinical data, and high-level content and presentation in a planned 351(k) BLA submission.

A copy of the official minutes of the teleconference 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) 402-6612.

Sincerely,

*{See appended electronic signature page}*

Claire Myers, Ph.D.  
Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes

“Pfizer response to FDA prelim comments\_IND\_117038 BPD2 13Feb2017.pdf”



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** Biosimilar Biological Product Development (BPD) Type 2  
**Meeting Date and Time:** Monday, February 13, 2017, 12:00PM – 1:00PM  
**Meeting Location:** Teleconference  
**Application Number:** IND 117038  
**Product Name:** PF-06439535  
**Proposed Indication:** PF-06439535 is being developed for the same indications as approved for US-licensed Avastin  
**Sponsor Name:** Pfizer Inc. (Pfizer)  
**Meeting Chair:** Steven Lemery, M.D., M.H.S.  
**Meeting Recorder:** Claire Myers, Ph.D.

**FDA ATTENDEES**

Patricia Keegan, M.D., Division Director, DOP2/OHOP  
Steven Lemery, M.D., M.H.S., Clinical Team Leader, DOP2/OHOP  
Sandra Casak, M.D., Clinical Reviewer, DOP2/OHOP  
Thomas Gwise, Ph.D., Deputy Division Director, DBV/OB  
Lisa Rodriguez, Ph.D., Statistical Team Leader, DBV/OB  
Jonathon Vallejo, Ph.D., Statistical Reviewer, DBV/OB  
Li Xing, Ph.D., CMC-Statistical Team Reviewer, OB/DBVI  
Sarah Schrieber, Pharm.D., Clinical Pharmacology Team Leader, DCPV/OCP  
Emily Wearne, Ph.D., Nonclinical Reviewer, DHOT/OHOP  
Chana Fuchs, Ph.D., Product Quality Team Leader, OBP/OPQ  
Yan Wang, Ph.D., Product Quality Reviewer, OBP/OPQ  
Anne Rowzee, Ph.D., Science Policy Analyst, TBBS/OND  
Sue Lim, M.D., Team Leader, TBBS/OND  
Tyree Newman, Regulatory Project Manager, TBBS/OND  
Leila Hann, Regulatory Project Manager, TBBS/OND  
Marlene Schulz-DiPalo, Biosimilar Program Analyst, OBP/OPQ  
Otto Townsend, Pharm.D., Safety Evaluator, DMEPA/OSE  
Latonia Ford, Safety Regulatory Project Manager OSE  
Nataliya Fesenko, R.Ph., Regulatory Health Project Manager, DOP2/OHOP  
Claire Myers, Ph.D., Regulatory Health Project Manager, DOP2/OHOP

## **SPONSOR ATTENDEES**

Beverly Ingram, Ph.D., Portfolio Lead Biosimilars Regulatory Affairs  
Thomas Porter, Ph.D., Research Fellow  
Rebecca Ingram, Principal Scientist Formulation  
Ben Grunder, Senior Scientist  
Cheryl Li, PhD Clinical Pharmacology Lead  
Raheel Shafi, M.D. Safety Risk Lead  
Duo Zhou, Statistician

## **BACKGROUND**

### **Regulatory**

On November 30, 2016, Pfizer Inc. (Pfizer) submitted a Biosimilar Biological Product Development Type 2 meeting request and meeting package. The meeting request was granted as a Biosimilar Biological Product Development (BPD) Type 2 Meeting based on the proposed questions requiring review of available data and targeted advice on specific development questions for PF-06439535. The purpose of the requested meeting is to discuss questions posed by Pfizer regarding the CMC/stability, clinical data, and high-level content and presentation questions for a planned 351(k) BLA submission.

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).

### **Chemistry, Manufacturing, and Controls (CMC)**

Pfizer's analytical biosimilar development program for PF-06439535 has been discussed through numerous communications. This meeting package includes a follow-up on previous discussions between FDA and Pfizer regarding the tier assignment and use of experimentally derived extinction coefficients for assigning protein concentration.

Pfizer is also seeking an agreement on the contents of the drug product stability data package to be included in the BLA in support of the requested expiration dating for the 100 mg/vial and 400 mg/vial presentations of PF-06439535.

### **Clinical**

The results of two clinical studies for PF-06439535 will be submitted in the BLA.

B7391001 is a PK similarity study that enrolled 102 healthy volunteers to establish PK similarity between PF-06439535 and US-licensed Avastin, between PF-06439535 and EU-approved bevacizumab, and between EU-approved bevacizumab and US-licensed Avastin. Analysis of this study is complete and Pfizer will submit the data from this study in the BLA.

Study B7391003 is an ongoing multinational, double-blind, randomized (1:1), comparative clinical trial evaluating the clinical effects of paclitaxel and carboplatin in combination with PF-06439535 or EU-approved bevacizumab in patients with advanced unresectable or metastatic non-

squamous NSCLC. The primary objective of Study B7391003 is to compare the confirmed objective response rate (ORR) by Week 19 following treatment with PF-06439535 in combination with paclitaxel and carboplatin to EU-approved bevacizumab plus paclitaxel and carboplatin in patients who have not received previous treatment for advanced NSCLC. The ORR must be confirmed 6 weeks after week 19, and is evaluated using RECIST v1.1. Secondary endpoints include duration of response, 1-year progression-free survival rate, and 1-year survival rate from randomization.

To show PF-06439535 is statistically equivalent to EU-approved bevacizumab, Pfizer will test the relative risk (RR) using two one-sided hypothesis tests. The sample size was calculated based on a margin for RR which maintained 43% of the two-sided 95% CI lower bound of the effect size based on the historical ORR data based on the meta-analysis treatment estimate of bevacizumab plus chemotherapy over chemotherapy alone based on a log scale (or about 50% on the linear scale). This approach was previously agreed upon during a BPD Type 3 meeting held April 15, 2015.

The following chart shows Pfizer’s proposal for data submission from Study B7391003 in the original BLA submission and in an amendments to the BLA during review.

	Primary Endpoint	Secondary Endpoints						
		Safety	DOR Rate	1-yr PFS Rate	1-yr OS Rate	Immunogenicity		PK
						Week 25	1-yr	
Initial BLA	100%	>66% (plus at least 6 months safety data in remaining patients)	>66%	>66%	>66%	100%	>66%	100% descriptive statistics up to week 25
4-month post (to coincide with 4-month Safety Update)	100%	100%	100%	100%	100%	100%	100%	100% descriptive statistics up to 1 yr and 100% Pop PK

DOR = Duration of Response; MAA = Marketing Authorisation Application; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; yr = year.

## DISCUSSION

### CMC

1. *Following a BPD3 meeting for PF-06439535 on April 15, 2015, the tier assignment for protein concentration remains to be confirmed. The rationale for assigning protein concentration for bevacizumab-Pfizer to Tier 2 is presented herein (Table 2 [of the meeting package]).*

*Can the Agency provide feedback on (a) the rationale and the assignment of protein concentration to Tier 2 and (b) use of the specific absorption coefficient of PF-06439535 which has been experimentally determined when calculating protein concentration?*

**FDA Response:** The assignment of protein concentration to Tier 2 for PF-0643953 is acceptable. FDA agrees that the absorption coefficients used to calculate the concentration of PF-06439535, US-licensed Avastin and EU-approved bevacizumab will be independently experimentally determined. FDA understands that results from this determination will inform on the extinction coefficient used for PF-06439535 protein concentration analysis. In the original BLA submission, include a description and justification of the experimental method and formulas used to determine the extinction coefficient. Use of an extinction coefficient determined from the labeled protein concentration in the package insert of the reference product as the known protein concentration is not appropriate.

**Pfizer Reply received via email February 13, 2017:** Refer to Pfizer's responses, attached.

**Discussion during the Meeting:** FDA clarified that Pfizer's plan for using the absorption coefficient of  $1.65 \text{ (mg/mL)}^{-1} \text{ cm}^{-1}$ , which is the specific absorption coefficient determined from the package insert concentration for US-licensed Avastin, is acceptable because it is within the experimental results as identified in Table 1 of Pfizer's reply. For other products, the use of an extinction coefficient determined from the labeled protein concentration on the package insert of the reference product may not be appropriate if experimentally determined extinction coefficients are different. The selected extinction coefficient used to determine the protein concentration for each product should be justified.

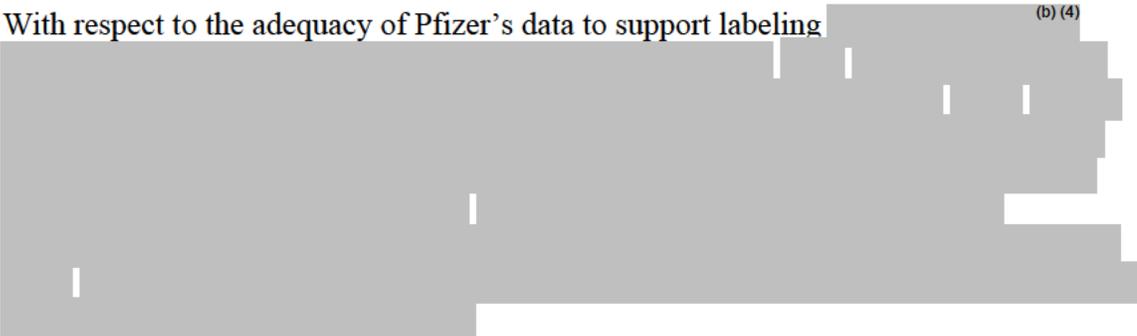
2. *Comprehensive stability data for PF-06439535 drug product at recommended storage (2-8°C) up to (b) (4) months for 1 drug product lot and 23 months for 5 other lots, followed by storage up to a maximum of 30°C for a single period of up to 1 month will be available at the initial submission, and further updated for 5 drug product lots at the 120 day update (Figure 1 [of the meeting package]). These data will be used to support storage at (b) (4) on the label. Does the FDA have any feedback on the stability data provision and data package?*

**FDA Response:** FDA does not agree with Pfizer's proposal to submit the data from 5 DP lots as part of the 120 day safety update. However, FDA may request a "simple stability update" during the course of the 351(k) BLA review to enable assessment of data from

additional timepoints. A simple stability update should include stability data and analyses performed under the same conditions and for the same drug product lots in the same container closure system(s) as described in the stability protocol and as provided in the original submission.

Regarding Pfizer's proposal to request (b) (4) month expiration dating, the product shelf life will be assessed based on the data in the original BLA submission. Data from 100 mg/vial and 400 mg/vial presentations will be necessary for assessment of product stability in each presentation and for setting an expiration date for each presentation. Include these data in the original BLA submission or in an amendment to the BLA submitted no later than 30 calendar days after the submission of the original application. The acceptability of a (b) (4) month shelf life for both the 100 mg and 400 mg presentations will be a review issue. In addition, it is not clear that the SE-HPLC assay can detect larger aggregates that may form during storage of the DP. Additional assays for detection of subvisible particles should be added to the stability protocol. FDA also suggests that Pfizer include CGE under non-reducing conditions to the stability protocol.

With respect to the adequacy of Pfizer's data to support labeling (b) (4)



**Discussion during the Meeting:** Pfizer acknowledged FDA's comments; there was no further discussion of this item during the meeting.

### Clinical

- Pfizer's initial BLA submission will be supported by 2 clinical studies (Table 1 [of the meeting package]): the completed PK study B7391001 and the on-going comparative clinical study B7391003. It is proposed that the initial BLA will include data from the completed PK study and the following data from the ongoing comparative clinical study: 1) data for all subjects through week 25, including primary efficacy endpoint, and 2) secondary endpoints data at 1 year for available subjects (comprising >66% of subjects).*

*Complete secondary endpoint data from the remaining subjects will be subsequently provided at the time of the 4-month Safety Update. The proposed data filing package from B7391003 study is shown in Table 5 [of the meeting package]. In order to execute this submission strategy, limited team members will be unblinded following the completion of the primary endpoint.*

*Does the agency agree and have any feedback with this submission approach?*

**FDA Response:** In the original BLA submission, Pfizer must include all data necessary to support the finding that PF-06439535 has no clinically meaningful differences from US-licensed Avastin, i.e., a complete submission to facilitate FDA's review. Confirm that the original BLA submission will contain complete safety data for all patients in Study B7391003, encompassing all planned cycles of chemotherapy in combination with PF-06439535 or EU-approved bevacizumab.

**Pfizer Reply received via email February 13, 2017:** Pfizer would like to clarify that the initial BLA will contain complete safety data for all patients for all planned cycles of the chemotherapy combination phase (i.e. through Week 25) as requested by the FDA in the preliminary response. In addition, the initial BLA will contain complete efficacy/primary endpoint, immunogenicity, and PK concentration data for all patients for the planned cycles of the chemotherapy combination phase (i.e. through Week 25). Furthermore, current projections estimate that the initial BLA will contain complete secondary endpoint data for approximately 75% of patients beyond the chemotherapy combination phase. Pfizer believes that this data package contains the necessary data to support the conclusion of no clinically meaningful difference between the proposed biosimilar and the reference product. To execute the initial BLA, limited team members will be unblinded following completion of the primary endpoint/chemotherapy combination phase.

At the time of the 4-month safety update, Pfizer will provide supplemental secondary endpoint data for the remainder ~25% of patients beyond the chemotherapy combination phase. These limited additional data are not expected to meaningfully change any of the safety, immunogenicity, or efficacy conclusions regarding similarity between the proposed biosimilar and the reference product.

**Discussion during the Meeting:** FDA concurs with Pfizer's proposed approach.

4. *Does the Agency agree that providing the datasets in Pfizer Data Standard is acceptable?*

**FDA Response:** Although Pfizer may submit datasets using the Pfizer Data Standard, FDA strongly recommends submission of datasets using CDISC standards. If Pfizer chooses to submit data in Pfizer's standard format, FDA encourages Pfizer to follow CDISC standards as much as possible. In addition, FDA encourages Pfizer to submit a mock dataset of the clinical data for FDA to comment on the proposed format and contents.

**Discussion during the Meeting:** Pfizer acknowledged FDA's comments; there was no further discussion of this item during the meeting.

## Regulatory

5. *Does the agency concur with Pfizer's proposal to provide in Module 5.3.5.3, a mapping document that provides the reviewer with all the necessary hyperlinks to relevant content in other parts of the dossier (e.g., CSRs and Module 2.7.4)?*

FDA Response: Yes, this proposal appears acceptable; however, FDA recommends that Pfizer provide a mock-up of Module 5.3.5.3 for review and comment.

**Pfizer Reply received via email February 13, 2017:** Pfizer acknowledges Agency's comment. Per FDA's recommendation, please see [in the attachment] a mock-up of Module 5.3.5.3 (Figure 1 ISE and Figure 2 - ISS) for FDA's review and comment. This mock-up is provided as an exemplar of the formatting and layout only. The specific headings and content will be amended for the BLA submission. Pfizer would welcome Agency feedback on the mock-ups as part of the final meeting minutes but additional discussion during the meeting is not needed.

**Discussion during the Meeting:** FDA stated that the proposal appeared to be acceptable; however FDA advised that the format and content of Pfizer's 351(k) application should be revisited during a BPD Type 4 meeting prior to submission of the BLA.

6. *Does the agency concur with Pfizer's proposal to 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: Pfizer's proposal may be acceptable; however, FDA is unclear what is meant by a "simplified" Module 2.5. FDA recommends that Pfizer provide a mock-up of Module 2.5 for review and comment.

**Pfizer Reply received via email February 13, 2017:** Pfizer acknowledges Agency's comment. Pfizer would like to clarify the meaning of "simplified Module 2.5" as a mapping document including hyperlinks that refer the reader to other parts of the submission that correspond to the specific sections of Module 2.5. Pfizer's intent is to limit redundancy and streamline the submission.

Per FDA's recommendation, please see [in the attachment] a mock-up of Module 2.5 for FDA's review and comment (Figure 3). This mock up is provided as an exemplar of the formatting and layout only. The specific headings and content will be amended for the BLA submission. Pfizer would welcome Agency feedback on the mock-up as part of the final meeting minutes but additional discussion during the meeting is not needed.

**Discussion during the Meeting:** FDA recommended that Pfizer include an appendix in Module 2.5 containing the scientific justification for extrapolation of use to indications not studied.

## **ADDITIONAL COMMENTS**

### **Statistics**

7. The proposed BLA should contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of investigator assessed PFS event or censoring and variables for subgroup analyses, etc. Variables used for any sensitivity analyses should be included as well.

**Discussion during the Meeting:** Pfizer acknowledged FDA's comments; there was no further discussion of this item during the meeting.

8. Include in your original BLA submission:
  - a. SAS programs that produced all efficacy results
  - b. All raw as well as derived variables in .xpt format
  - c. SAS programs by which the derived variables were produced from the raw variables
  - d. Results of any interim analysis if performed

**Discussion during the Meeting:** Pfizer acknowledged FDA's comments; there was no further discussion of this item during the meeting.

### **Clinical Pharmacology**

9. 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 efficacy, 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.

**Discussion during the Meeting:** Pfizer acknowledged FDA's comments; there was no further discussion of this item during the meeting.

## **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.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

Please be advised that if an original 351(k) BLA is submitted on or after October 1, 2017, the application will be subject to “the Program” under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), as applicable. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on BsUFA II and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm>.

## **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](mailto: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>

### **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>.

### **ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

### **ATTACHMENTS AND HANDOUTS**

“Pfizer response to FDA prelim comments\_IND\_117038 BPD2 13Feb2017.pdf”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CLAIRE E MYERS  
03/05/2017