

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761072Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114828

MEETING MINUTES

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Robert Schaum, PhD
Director, Worldwide Regulatory Strategy

Dear Dr. Schaum:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06438179.

We also refer to the meeting between representatives of your firm and the FDA on November 22, 2016. The purpose of the meeting was to discuss the overall content, format, and procedural considerations for the planned 351(k) BLA submission for PF-06438179, a proposed biosimilar to US-licensed Remicade (infliximab).

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

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CAPT, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4 Meeting

Meeting Date and Time: November 22, 2016 2:00 – 3:00 P.M.
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: IND 114828
Product Name: PF-06438179
Indication: PF-06438179 is being developed for the same indications as approved for US-licensed Remicade
Sponsor/Applicant Name: Pfizer Inc. (Pfizer)

Meeting Chair: Dr. Badrul Chowdhury, Director
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Rosemarie Neuner, MD, Clinical Reviewer, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Gregory Levin, PhD, Biometrics Team Leader, Division of Biometrics II (DBII)
Ginto Pottackal, PhD, Biometrics Reviewer, DBII
Chris Downey, PhD, Team Leader, Division of Biotechnology Review and Research II (DBRRII)
Patrick Lynch, PhD, Product Quality Reviewer, DBRRII
Colleen Thomas, PhD, Quality Assessment Lead (Actg), Division of Microbiology Assessment (DMA)
Monica Commerford, PhD, Product Quality Microbiology Reviewer, DMA
Meiyu Shen, PhD, Biometrics Team Leader, Division of Biometrics VI
Yu-Ting Weng, PhD, Biometrics Reviewer, Division of Biometrics VI
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII)
Janice Weiner, JD, MPH, Senior Regulatory Counsel, Office of Regulatory Policy, Division of Regulatory Policy I (ORP/DRP1)
Sue Lim, MD, Team Leader, OND Therapeutic Biologics & Biosimilars Staff (TBBS)
Anne Rowzee, PhD, Reviewer, TBBS
Leila Hann, Regulatory Project Manager, TBBS
Tyree Newman, Regulatory Project Manager, TBBS

SPONSOR ATTENDEES:

Joseph McClellan (Asset Lead)
Ana Claudia Ianos (Safety Lead)
John Orazem (Biostatistics lead)
Joan Kwong (Regulatory CMC)
Bob Repetto (Regulatory CMC)
Navayath Shobana (Regulatory CMC)
Robert Schaum (Regulatory)
Janett Mugaburu-Richards (Regulatory)
Karen Rule (Analytical R&D)

Joining by phone:

Robert Wolk (Clinical)
Lea Sewel (Clinical)
Ramesh Palaparthi (Clinical Pharmacology Lead)
Vatche Kalfayan (Clinical Operations)
Hugh Conlon (Regulatory CMC)
Carol Kirchhoff (Biomanufacturing Sciences))
Ling Gu (Analytical R&D)
Chengyu Gao (Regulatory)
Aili Cheng (Analytical R&D)
Carol Hervey (Project management)
Steven Hua (Biostatistics)
Min Zhang (biostatistics)

Background:

Pfizer requested a BPD Type 4 meeting to discuss overall content, format, and procedural considerations for the planned 351(k) BLA submission. A BPD Type 2 meeting was held July 8, 2016, to discuss CMC, the draft statistical analysis plan, as well as high level questions about the format and content for the BLA. Pfizer plans to submit the BLA in February 2017.

After review of the briefing package, FDA sent preliminary responses to Pfizer's questions in an emailed letter dated November 17, 2016. In an email sent evening of November 21, 2016, Pfizer provided their comments or additional questions which are incorporated into the body of the minutes as well as provided as an Attachment at the end of the minutes.

Below are the sponsor's questions from the briefing package in *italics*; FDA's responses (meeting preliminary comments) in normal font; and Pfizer's November 21, 2016, emailed responses also noted in *italics*. A summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

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 (PHS) Act.

QUESTIONS AND RESPONSES

Question 1

Does the FDA have any feedback on the proposed structure and format of the PF-06438179 351(k) BLA as presented in Appendix 4 of the Meeting Package Materials such that it meets the Agency's expectations for e-CTD submission?

FDA response:

The proposed structure and format of your 351(k) BLA for PF-06438179 is acceptable. Consider incorporating a discussion of extrapolation into the discussion of known and plausible mechanisms of action.

Refer to FDA Additional Product Quality Microbiology Comments section below.

Pfizer's 11/21/16 emailed response:

The topic of extrapolation and known and plausible mechanism of action for each indication is covered in 2.2 Introduction. No additional discussion is required.

Question 2

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 5 in CTD Section 1.12.11 such that it meets the Agency'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:

Your proposed roadmap for the 351(k) BLA appears reasonable. As mentioned above, consider consolidating the discussion of extrapolation with the discussion of known and plausible mechanism(s) of action for each indication being sought.

Pfizer's 11/21/16 emailed response:

The topic of extrapolation and known and plausible mechanism of action for each indication is covered in 2.2 Introduction. No additional discussion is required.

Question 3

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

FDA response:

We have no additional comments at this time.

Pfizer's 11/21/16 emailed response:

No additional discussion is required. However, Pfizer clarifies that only the supplementary CSR for Treatment Period 2 (week 54) of study B5371002 will be provided for the 120-Day safety update.

Discussion:

FDA stated that Pfizer's proposal sounded acceptable and asked if data from the transition study will be included with the BLA submission.

Pfizer responded that they planned to include week 30 data with the BLA submission and provide week 52 data with the 120 safety update. Pfizer added that due to re-randomization, there is a partial lack of continuity between TP1 and TP2 in all arms. The treatment periods will not be integrated across the treatment periods but presented separately in their respective CSRs.

FDA stated that they will look at the data separately, so Pfizer's proposal would be acceptable.

Question 4

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 6?

FDA response:

Your proposed organization of CTD Section 3.2.R.3 appears reasonable. We note that for some methods, you intend to provide tabulated data from 53 US-licensed Remicade, 59 EU-approved Remicade, and 15 PF-06438179 lots in an appendix (3.2.R.3.5). Ensure that all data from each lot tested by each method is included in your 351(k) BLA. See FDA response to Question 6 below.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

Question 5

Does FDA have any feedback on the proposed presentation of summary information (Appendix 6) regarding the lots of PF-06438179 and infliximab- US/infliximab-EU used in the analytical biosimilarity assessment?

FDA response:

You report that section 3.2.R.3.1.2 will include discussion on the number of lots used for the similarity assessment and criteria used to select lots for the similarity assessment. We agree with this approach and recommend that you include summary information on the use of each manufactured drug substance batch and drug product lot of PF-06438179 as well as each purchased lot of US-licensed Remicade and EU-approved Remicade. Information should be provided on the studies conducted with each lot (e.g., analytical similarity, nonclinical, clinical, and stability studies). For each drug product lot of PF-06438179, you should provide information on the corresponding drug substance batch(es), including the batch number and manufacture date. Provide a list of all lots that were selected to be included in (or excluded from) specific analytical similarity studies along with a justification. Any criteria being used to select lots for studies should be clearly defined.

Pfizer's 11/21/16 emailed response:

The discussion on number of lots of reference product and comparator used for similarity assessment is provided in 3.2.R.3.1.2. The information on the drug substance and drug product lots used for similarity assessment is provided in the appendix 3.2.R.3.5. All the PF-06438179 drug substance and drug product lots manufactured have been used for similarity assessment. Information on the batch number, manufacturing date and purpose (e.g. stability) of the drug substance batch used to manufacture a drug product lot is provided in the 3.2.P.5.4 Batch Analyses and 3.2.S.4.4 Batch Analyses respectively. Section 3.2.P.2.3 Lot Genealogy outlines the PF-06438179 materials used in nonclinical and clinical studies. Section 3.2.R.3.5 Appendix lists the PF-06438179 DS batches and DP lots, infliximab-US and infliximab-EU lots used in non-clinical and clinical studies.

Question 6

Does FDA have any feedback on the proposed presentation of results in CTD Section 3.2.R.3 (Appendix 6) including summary data tables?

FDA response:

The overall approach to presentation of results outlined in Appendix 6 appears reasonable. We have the following comments:

- a) For each analytical method, representative data should be presented in graphical format (e.g., chromatograms, electropherograms, peptide maps, gels, bar graphs or other easy-to-read formats), in addition to the proposed summary table format. Be sure that the presentation of the data enables direct comparison of the results from each individual lot and clearly delineates the US-licensed Remicade (i.e., reference product) lots, and EU-approved Remicade lots, from lots of PF-06438179.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

- b) Your proposal to include summary data tables appears reasonable, provided that for each assay you also submit results from individual product lots that are not averaged or otherwise combined. Where applicable, summary data tables should include information on the number of lots and the standard deviations for quality attribute values that are averaged or combined from multiple lots. Ideally, summary data (e.g., mean and standard deviation) would also be provided in the tables with results from individual lots.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

- c) Table 11 in Appendix 6 of your meeting package proposes to present data for multiple quality attributes from 53 lots of US-licensed Remicade, 59 lots of EU-approved Remicade, and 15 lots of PF-06438179 in Section 3.2.R.3.5 of your future BLA submission. Instead, we recommend that in your BLA submission, you provide one table using the format of Table 11 for each of the three products separately (i.e.,

one table for PF-06438179, US-licensed Remicade, and EU-approved Remicade, respectively). Also, add a column titled “Analysis date” to each table.

Pfizer’s 11/21/16 emailed response:

Although data are submitted in one table, they are arranged such that all infliximab-US data is presented first, followed by infliximab-EU and then followed by PF-06438179 data, which should address the FDA request. Does the agency agree this is an acceptable approach?

Discussion:

FDA stated one table would be acceptable and requested that an “Assay date” column be added (not “Analysis date”).

Question 7

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

FDA response:

In principle, we agree with your proposed locations in the 351(k) BLA for analytical method descriptions as provided in Table 5 of the briefing document. The adequacy of information provided in the method descriptions will be a review issue. Additionally, we have the following comments.

- a) You propose to provide cross-references to descriptions of routine analytical methods located in Sections 3.2.S.4.2 and 3.2.P.5.2, as applicable. You may also consider providing cross-references to additional characterization method descriptions for instances where the same method is used in multiple Sections (e.g., cross-references in Section 3.2.S.3.1 to summaries already provided in Section 3.2.R.3). However, you will need to make clear whether any modifications to the method may apply when used for multiple purposes. Refer to our comment c below.
- b) To facilitate review, please include hyperlinks wherever cross-references to descriptions of analytical methods are utilized.
- c) Analytical method descriptions should include detailed information on manipulation of the test articles, including US-licensed Remicade and EU-approved Remicade. If the formulation of these products has been modified for evaluation of analytical similarity, an assessment of the impact of such a modification on the quality attributes of the products should be included and justified.

Pfizer’s 11/21/16 emailed response:

Pfizer acknowledges Agency’s comment. No additional discussion is required.

Question 8

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

FDA response:

We agree with your proposal to include analytical method validation summaries for routine release test methods in Sections 3.2.S.4.3 or 3.2.P.5.3, and characterization qualification reports in Section 3.2.R.3. The adequacy of information provided in these Sections will be a review issue.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

Question 9

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

FDA response:

Referencing drug product facility DMFs (b) (4) validation data is not sufficient if the information in the DMF is not product-specific. For example, the application should clearly indicate which (b) (4) operations, etc. are relevant to PF-06438179 production. The application should clearly explain how the (b) (4) program covers the (b) (4) operations applicable to PF-06438179 production. 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.

Pfizer's 11/21/16 emailed response:

The Pfizer Puurs Type V DMF 7105 will be updated prior to the PF-064382179 BLA submission to include all the requested product-specific information. No discussion is required.

Question 10

Does the FDA have comments on the manufacturing schedule for PAIs 2-4 months after BLA filing?

FDA response:

Refer to FDA Additional Product Quality Microbiology Comments section below regarding information on pre-licensing inspections (comment 1). Note that the drug substance manufacturing facility should be in operation manufacturing PF-06438179 during months 2 – 3 of the review cycle. The drug product site should be in operation manufacturing PF-06438179 or performing similar (b) (4) processing operations on the fill line which is used to manufacture PF-06438179. Additionally, a manufacturing schedule for PF-06438179 drug substance and drug product should be provided in Module 1 of the 351(k) BLA submission.

Pfizer's 11/21/16 emailed response:

A tentative manufacturing schedule for drug substance and drug product is provided below. Based on this schedule and a planned BLA submission in mid-Feb 2017, Pfizer confirms that the drug substance manufacturing facility will be in operation manufacturing PF-06438179 during months 2-3 of the review cycle. Since (b) (4) (b) (4) is a CMO, Pfizer will work closely with (b) (4) to provide a final schedule of the individual production steps that will be available for observation during the PAI.

For drug product, Pfizer confirms that all areas of the drug product manufacturing facility involved in PF-06438179 manufacture will be in operation manufacturing PF-06438179 or performing similar (b) (4) processing operations on the fill line. For example, would filling operations for another product (e.g., another biosimilar, another biologic, or a small-molecule lyophilized product presented in a vial) on the fill line used to manufacture PF-06438179 be acceptable?

Discussion:

The FDA stated that a pre-license inspection of the drug product manufacturing site could be conducted during manufacture of a different product on the fill line used for PF-06438179 if the product is lyophilized, supplied in vials, and manufactured by (b) (4) operations similar to those used for PF-06438179. The product may be a biotech, biosimilar, or small molecule drug.

Does the FDA have any feedback on this plan for the drug product manufacturing schedule?

Manufacturing Site and Registration (FEI) Number	Responsibilities	Tentative manufacturing schedule
(b) (4)	Drug substance manufacture, in-process control testing, release testing	Drug substance manufacture: (b) (4)
Pfizer Manufacturing Belgium NV Rijksweg 12, Puurs, B-2870, Belgium (BEL) FEI: 1000654629	(b) (4) Drug product manufacture, primary packaging, release testing, secondary packaging and labeling	Drug product manufacture (PF-06438179 or similar (b) (4) processing operations on the fill line): Week of (b) (4)

Discussion:

FDA stated that the approximate proposed dates appear to be acceptable, but the BLA should include the complete breakdown of the manufacturing schedule. FDA

asked whether the two drug substance manufacturing runs scheduled for the week of (b) (4), would include (b) (4) operations.

Pfizer responded that that (b) (4) operations from one run and (b) (4) operations from the other run were scheduled for that week.

Question 11

The analytical work to confirm similarity of PF-06438179 and the reference product/comparator was conducted at the development sites in the USA and not at the manufacturing sites (except for a subset of release testing) listed in the BLA submission. Pfizer is seeking a mechanism to facilitate FDA review of raw data supporting the demonstration of analytical similarity, if required, and proposes (b) (4)

Does FDA have feedback on this proposal?

FDA response:

We do not agree with your proposal (b) (4). We may conduct pre-approval inspection(s) (PAI) of analytical similarity results at sites where raw analytical data were generated to support similarity between PF-06438179 and the reference and comparator products, and your approach would limit access to all the necessary information. Provide a listing of all sites where analytical similarity assessments were conducted and identify the testing sites for each method. Report this information in the 3.2.R, Regional section of your 351(k) BLA application.

With regards to review of analytical similarity data at manufacturing sites, including the drug substance contract manufacturing organization (CMO), our expectation is that relevant data generated at the manufacturing site (e.g. release and stability) will be made available during a PAI.

Pfizer's 11/21/16 emailed response:

The analytical similarity assessment has been supported by the Pfizer Research and Development organization, which is distributed across several locations. Pfizer's proposal is intended to make available all the data generated in support of the analytical similarity assessment and the relevant subject matter experts at a convenient location to facilitate the review. With Pfizer's proposal to conduct raw data audit at Silver Spring office, Pfizer do not limit access to data generated at the manufacturing sites (i.e. Pfizer Puurs and (b) (4)) during PAIs at the respective sites. As requested, a listing of all sites where analytical similarity assessments were conducted, including identification of the testing sites for each method will be provided in the 3.2.R section of the BLA.

Discussion:

FDA responded that the plan proposed by Pfizer could be acceptable, but they reserve the option to inspect developmental site laboratories. FDA will look at the list of sites and make an assessment after BLA submission.

Pfizer asked what should be prepared for a PAI.

FDA responded that they may go to the lab sites to speak to operator(s) and review raw data for specific assays relevant to the analytical similarity analyses.

Question 12

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

FDA response:

Your proposal is acceptable. That being said, although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required for studies that start before December 17, 2016, we strongly encourage you to use the FDA supported data standards for the submission of your BLAs.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

Question 13

Does FDA concur with the proposed labeling concept for PF-06438179 to support the 351(k) BLA submission [REDACTED] (b) (4)

FDA response:

We do not agree with your proposal [REDACTED] (b) (4). Refer to *Draft Guidance for Industry, Labeling for Biosimilar Products*, available at the following website: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges Agency's comment. No additional discussion is required.

Question 14

In view of the Agency's recent experience with proposed biosimilars for Remicade, and to assist in Pfizer's planning for a potential Arthritis Advisory Committee public hearing:

- a) *Can the Division comment on the potential need to hold an Arthritis Advisory Committee meeting to review the 351(k) application for PF-06438179, assuming the application meets the statutory requirements for licensure as a biosimilar product?*
- b) *Can the Division comment on the approximate timing of a decision to hold an Arthritis Advisory Meeting after submission of the 351(k) application for PF-06438179 (again assuming the application meets the statutory requirements for licensure as a biosimilar product)?*

FDA response:

Presuming no unexpected issues arise that warrant public discussion, it is unlikely that an Arthritis Advisory Committee meeting will be held to discuss your proposed 351(k) application. However, a decision to convene an Advisory Committee meeting would preliminarily be made by the time of filing, although such a decision would not be final, as issues may be identified upon detailed review.

*Pfizer's 11/21/16 emailed response:
Pfizer acknowledges Agency's comment. No additional discussion is required.*

FDA Additional CMC comments:

1. Antibody-mediated reverse signaling and induction of regulatory macrophages have been identified in the scientific literature as potential mechanisms of action for anti-TNF monoclonal antibody products.¹ In reverse signaling, the antibody cross-links or binds to membrane-bound TNF- α (mTNF) on cells and either induces apoptosis or inhibits secretion of pro-inflammatory cytokines depending on the target cell (type). Regulatory macrophages are postulated to play an important role in wound healing and gut homeostasis. Your analytical similarity assessment should compare the ability of PF-06438179 and of US-licensed Remicade and of EU-approved Remicade to elicit reverse signaling and induction of regulatory macrophages. The following should be included in your assessment:
 - a. A cell-based assay to evaluate either inhibition of cytokine production or apoptosis induction as a result of binding of the anti-TNF antibody to mTNF in a relevant cell model. You should use a sufficient number of PF-06438179 and US-licensed Remicade and EU-approved Remicade lots to obtain reliable estimates for the mean and variability of each product and analyze the data as a Tier 2 attribute.

*Pfizer's 11/21/16 emailed response:
Pfizer acknowledges Agency's comment. All the analytical similarity strategy and information to be presented as part of the BLA was developed in cooperation with the FDA in the course of BPD Type 3 and BPD Type 2 meetings. The strategy has not included the use of an assay to assess reverse signaling.*

As part of our comprehensive analytical and functional similarity assessments, a sensitive cell-based binding assay using mTNF transfected NS0 cell line and flow cytometry technology is used to evaluate the binding affinity of PF-06438179, infliximab-US, and infliximab-EU licensed product to cell surface mTNF. The data has been analyzed by Tier 2 statistics and confirms similarity in terms of mTNF binding. Secondary responses such as reverse signaling will occur with binding of infliximab to mTNF.

Consequently, we do not see value in developing an additional in vitro assay with a transfected cell line to show binding to cell surface mTNF which is followed by a reverse signaling apoptosis response. We look forward to further discussing this with the agency.

Discussion:

Pfizer asked FDA for rationale as to why a separate cell-based reverse-signaling assay was needed and for the value-added of such an assay.

FDA responded that although the binding data are important, it is also important to confirm the outcome of mTNF binding with functional assays that can measure either cytokine production or apoptosis. The ADCC and CDC assays measure

¹ Olesen, CM, M Coskun, L Peyrin-Biroulet, O Haagen Nielsen, 2016. Mechanisms Behind Efficacy of Tumor Necrosis Factor Inhibitors in Inflammatory Bowel Diseases. *Pharmacology & Therapeutics*, 159:110-119. <http://dx.doi.org/10.1016/j.pharmthera.2016.01.001>.

effector activity. Therefore, FDA still expects to see reverse-signaling functional assays.

Pfizer noted that conduction of such assays will impact timing of the BLA submission and proposed that the results be submitted at the planned 120 day safety update.

FDA agreed to review the reverse signaling cell-based assay results submitted during the review cycle as an amendment to their BLA provided that Pfizer submit the results no later than 120 days after BLA submission.

- b. A cell-based assay to evaluate induction of regulatory macrophages. A sufficient number of PF-06438179 and U.S.-licensed Remicade and EU-approved Remicade lots should be evaluated to obtain reliable estimates of the activity of both products.

Pfizer's 11/21/16 emailed response:

We have evaluated the induction of regulatory macrophages by PF-06438179, infliximab-US, and infliximab-EU licensed product in a mixed lymphocyte reaction (MLR) assay. The MLR assay assesses infliximab-induced regulatory macrophages and their immunosuppressive ability to inhibit T cell proliferation. [Vos AC, Wildenberg ME, Duijvestein M, et al. Anti-tumor necrosis factor-alpha antibodies induce regulatory macrophages in an Fc region-dependent manner. Gastroenterology 2011; 140:221-30]

Five lots each of PF-06438179, infliximab-US, and infliximab-EU licensed product were analyzed and demonstrated comparable activity in a dose-dependent manner in the MLR assay. Does this satisfy the Agency's expectation?

Discussion:

FDA responded that the information provided appears to be reasonable. The sponsor will need to provide a justification for the selected method in the BLA submission. The suitability of the assay to evaluate induction of regulatory macrophages will be a review issue.

- c. An evaluation of the binding affinity of US-licensed Remicade, EU-approved Remicade, and PF-06438179 to mTNF on the surface of relevant cell types. The data may be analyzed as a Tier 3 attribute.

Pfizer's 11/21/16 emailed response:

A cell-based binding assay using mTNF-transfected NS0 cell line and flow cytometry technology will be provided to evaluate the binding affinity of PF-06438179, infliximab-US, and infliximab-EU licensed product to cell surface mTNF.

2. In Appendix 6 - Overview of Section 3.2.R.3 Comparative Physicochemical and Functional Assessment, you report that analytical similarity evaluations will include data from 15 PF-06438179 (6 drug substance, 8 drug product and 1 reference material) batches/lots. Our expectation is that each independent lot should contribute one value for each attribute being assessed. We advise you that for the purpose of evaluating analytical similarity, we do not consider drug product lots to be independent of their corresponding drug substance batches.

Additionally, we do not consider different drug product lots produced from the same drug substance batch to be independent. As you plan your submission, please ensure that your statistical analyses of analytical similarity include only independent lots or batches of PF-06438179. Clarify the number of independent lots you will be including for each assay in your statistical evaluation to support that PF-06438179 and US-licensed Remicade are highly similar.

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges the Agency's comment. Pfizer's similarity assessment strategy was to include PF-06438179 drug substance batches (DS) and drug product (DP) lots based on the guidance provided by the Agency at the BPD2 meeting held on January 29, 2016. Please see excerpt from the meeting minutes below. Pfizer has included seven DS batches, eight DP lots and one reference material in the similarity assessment without preselection. No DP lots were excluded based on common source DS. This ensured that a minimum of 10 lots of PF-06438179 data were available for similarity assessment.

53 lots of innovator US were purchased on the open market and included in the similarity assessment without preselection. None of the innovator lots were excluded based on the possibility that they were derived from a common DS batch.

Additionally, Pfizer has high confidence in the PF-06438179 DS manufacturing process; the control strategy in place has yielded highly reproducible DS batches (see 3.2.S.4.4 Batch Analysis Table below), and hence Pfizer proposes to provide the statistical similarity assessment in the BLA in accordance with the agreed approach of the January 29, 2016 meeting with FDA.

Discussion:

Pfizer referenced FDA meeting minutes from the BPD2 meeting held in January 2016 that indicated agreement between FDA and Pfizer to include both DS and DP lots in analytical similarity assessments.

FDA responded that in previous meetings the relationship between the DS and DP lots had not been clear, but maintained that it is acceptable to evaluate independent DS batches in analytical similarity studies. The following points should be noted for statistical analysis purposes:

- a) FDA expects that statistical analyses for analytical similarity will include only one data point per independent batch or lot. Different DP lots produced from the same DS batch are not considered to be independent. DP lots from pooling different DS batches are also not considered independent data points.**
- b) FDA noted that most of the variability seen in quality attributes is sourced to the DS and not expected to change substantively between DS and DP lots. The example was given that attributes including binding to TNF alpha, ADCC, and glycosylation are not likely to change with a well-controlled DP manufacturing process.**
- c) Also, although there can be variability between DP lots manufactured from the same DS batch, this DP-DP lot variability is less than the DS-DP lot variability that results from DP lots which come from different DS batches. Therefore, the concern**

with using related DP lots in statistical analyses is that this will skew lot-to-lot variability measurements.

- d) Reference product lots should have ideally been purchased over a wide spread of time to decrease possible correlation of purchased lots from the same DS lot.**
- e) FDA suggested that it may be acceptable to evaluate non-commercial scale DS batches in the analytical similarity assessment provided that the DS manufacturing process resembles that of the commercial process. FDA did not specify a particular number of lots needed for the similarity assessment.**

Pfizer noted that the variability of PF-06438179 is much lower than that of the reference product in their experience and raised the possibility that the variability of the reference product is under-estimated relative to the proposed biosimilar variability. Pfizer was concerned that this discrepancy inflated the Type I error, and reduced the likelihood that PF-06438179 would pass Tier 1 testing.

FDA stated that Pfizer's analyses cannot be based on the assumption that reference product lots are not independent and that reference product variability is under-estimated since there is no way to know the relationship of reference product lots tested. In contrast, the relationships and independence of PF-06438179 lots tested can be definitively known.

Pfizer also requested guidance on the following in conducting a similarity assessment:

- **selecting between 2 DP lots derived from the same DS lot, when both DP lots have been used in clinical studies,**
- **selecting the DP lot when multiple dosage forms are made from a single DS (not specific to this program).**

Pfizer expressed concern that with the 351(k) BLA submission planned for February 2017 and with less than 10 independent data points in the analytical similarity assessment, the confidence interval to be used in the Tier 1 assessment may be lower than 90%. Pfizer asked if this would be considered a refuse-to file (RTF) issue.

FDA replied that this would not be considered a RTF issue, and subsequent communication(s) needed regarding statistical analyses of analytical similarity will be managed in a timely manner.

FDA Additional Product Quality Microbiology Comments:

To supplement the FDA feedback listed in Appendix 8 of your meeting package, we are providing additional updated product quality microbiology pre-BLA comments for you to consider in preparation of your 351(k) BLA submission.

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

Pfizer's 11/21/16 emailed response:

Pfizer acknowledges the Agency's comment. No further discussion is required.

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

- a.  (b) (4)
- b.
- c.
- d.
- e.
- f.
- g.
- h.

Pfizer's 11/21/16 emailed response:

All the points noted above will be addressed in the BLA either by provision of data requested or provision of other appropriate information. No further discussion is required.

3. The CMC Drug Product section of the BLA (Section 3.2.P) for PF-06438179 should contain validation data summaries to support the  (b) (4). For guidance on the type of data and information that should be submitted, refer to the 1994 FDA *Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.

- The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- a.
- b.
- c.
- d.
- e.
- f.
- g.
- h.

(b) (4)

Pfizer's 11/21/16 emailed response:

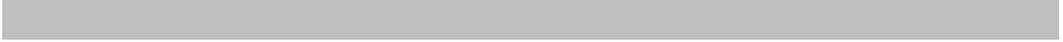
All the points noted above will be addressed in the BLA by provision of data requested, cross-reference to the Pfizer Puurs Type V DMF #7105, or provision of other appropriate information. No further discussion is needed.

- The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- a.
- b.
- c.
- d.
- e.

(b) (4)

f.  (b) (4)

g. 

Pfizer's 11/21/16 emailed response:

Points a, d, and g will be addressed in the BLA by provision of data requested or other appropriate information. Points b, c, e, and f pertain to facility and equipment information and will be addressed via cross-reference to the Pfizer Puurs Type V DMF 7105, which will include all the requested product-specific information and will be updated as appropriate during life cycle of the product. Does FDA agree with this approach?

Discussion:

Pfizer stated that they intend to update the DMF to include product-specific information prior to BLA submission and maintain the DMF for the lifecycle of the product. Pfizer asked if this approach would be acceptable.

FDA agreed with the sponsor's proposal to cross-reference product-specific information in the Pfizer Puurs Type V DMF 7105 to support the BLA. Regarding updates to the DMF during the lifecycle of the product, FDA noted that information in the DMF would be reviewed only when referenced by submissions to the BLA file, and should not be relied on to notify the Agency of changes to the DMF. Changes should be reported to the BLA file as appropriate, and a Letter of Authorization which references the relevant information in the DMF should be provided.

- The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

a.  (b) (4)

b. 

c. 

d.

(b) (4)

e.

Pfizer's 11/21/16 emailed response:

Points b, c, d, and e will be addressed in the BLA by provision of data requested or other appropriate information. For point a, verification of the container closure integrity method has been performed, and the information will be provided in the BLA. Further method verification involving a positive control defect size of $\leq 20 \mu\text{m}$ is being conducted and data will be provided when available.

Discussion (item a):

Pfizer indicated that they may not have the container closure integrity testing data ready for their planned mid-February 2017 BLA submission. Pfizer asked if they could provide these data during the BLA review. In response to FDA's request for a specific timeframe, Pfizer proposed to provide container closure integrity method verification data for the positive control defect size of ≤ 20 microns either in the initial BLA submission or no later than four months after initial BLA submission.

FDA agreed to the sponsor's proposal. Additionally, FDA stated that adequacy of the data requested (in parts 2 and 3 of the Additional Product Quality Microbiology comments and "other appropriate information") will be determined during review of the application.

Pfizer's 11/21/16 emailed Additional question for clarification:

Regarding the subject-level clinical data listings for our clinical studies, Pfizer will provide the BIMO subject-level clinical data listings for B5371002 (comparative efficacy study) as requested. However, is there a similar requirement for B5371001 (comparative PK study) which is a single-center study?

Discussion:

FDA stated that subject-level data (.xpt files) were required for the comparative PK study (B5371001). However, since the comparative PK study is a single-center study, the BIMO requirement is not applicable.

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.

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 (cdcr-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>

PRESCRIBING INFORMATION

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

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

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

Office of Scientific Investigations (OSI) Requests

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

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

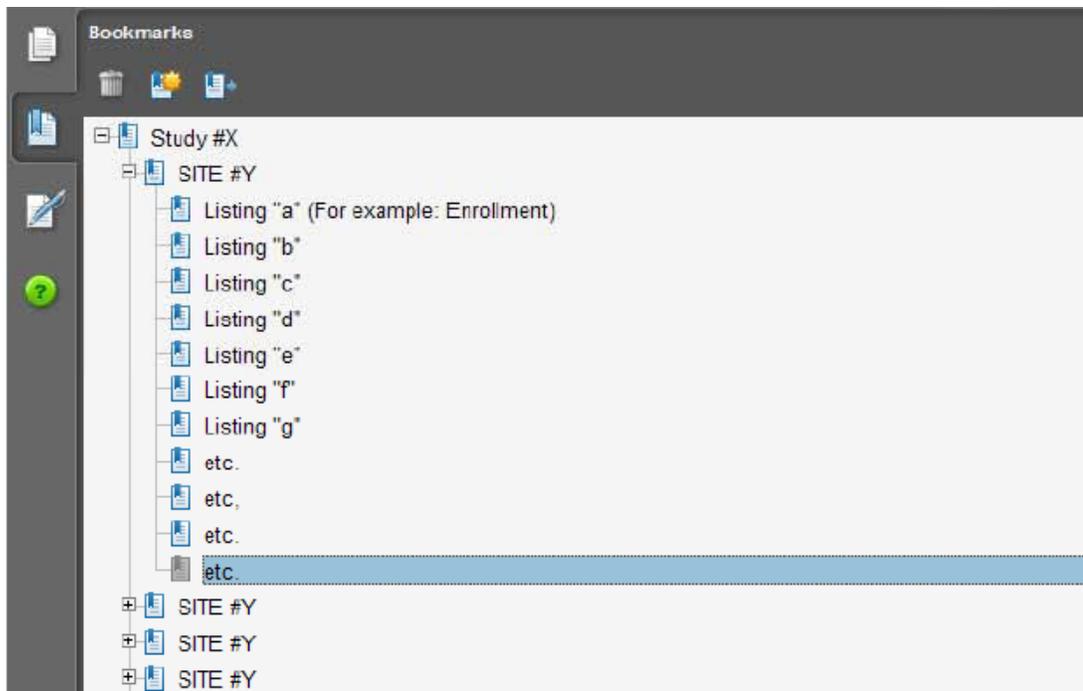
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

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

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



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

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

References:

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

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

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

ISSUES REQUIRING FURTHER DISCUSSION:

Pfizer submitted their minutes of the November 22, 2016, meeting that included post-meeting requests for clarifications. Responses to Pfizer's questions will be provided in a separate correspondence.

ATTACHMENTS AND HANDOUTS:

Pfizer's November 21, 2016, emailed responses to FDA's meeting preliminary comments begin on the next page.

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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.

/s/

CHRISTINE H FORD
01/06/2017



IND 114828

MEETING MINUTES

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Robert Schaum, Ph.D.
Director, Worldwide Regulatory Strategy

Dear Dr. Schaum:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06438179 (“infliximab-Pfizer”).

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2014. The purpose of the meeting was to discuss the adequacy of the functional, structural, and PK similarity data comparing PF-06438179 to the reference product (US-licensed Remicade) to support the “Phase 3” development plan.

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

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 3 Meeting

Meeting Date and Time: August 5, 2014 8:00 – 9:00 A.M.
Meeting Location: White Oak Building 22, Conference Room: 1415

Application Number: IND 114828
Product Name: PF-06438179 (“infliximab-Pfizer”)
Indication: PF-06438179 is being developed for indications same as approved for US-licensed Remicade (infliximab)

Sponsor/Applicant Name: Pfizer Inc. (Pfizer)

Meeting Chair: Badrul Chowdhury, Director
Meeting Recorder: Christine Chung, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Supervisory Associate Director, DPARP
Susan Limb, M.D., Clinical Team Leader, DPARP
Rosemarie Neuner, M.D., Clinical Reviewer, DPARP
Nikolay Nikolav, M.D., Clinical Team Leader, DPARP
Christine Chung, R.Ph., Regulatory Project Manager, DPARP
David Frucht, M.D., Ph.D., Team Leader, Division of Monoclonal Antibodies (DMA)
Kurt Brorson, Ph.D., Team Leader, Division of Monoclonal Antibodies (DMA)
Erik Read, Ph.D., Product Quality Reviewer, DMA
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCPII
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCPII
Ruthanna Davi, Ph.D., Biometrics Team Leader, Division of Biometrics II
Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel, Office of Regulatory Policy, Division of Regulatory Policy I (ORP/DRP1)
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics, OND Therapeutic Biologics & Biosimilars Team (TBBT)
Sue Lim, M.D., Senior Staff Fellow, TBBT
Carla Lankford, M.D., Ph.D., Science Policy Analyst, TBBT
Tyree Newman, Regulatory Project Manager, TBBT
Vivian Chen, Pharmacy Intern

SPONSOR ATTENDEES:

Clinical Immunology & Biomarkers	Claudio Carini
Director, Non-Clinical Statistics	Aili Cheng
Principal Scientist, Analytical R&D	Hugh Conlon
SVP, Biosimilars Chief Development Officer	Michael Corbo
Research Fellow, Reg Strategy & Compliance	Mazin Derzi
Senior Director, Pharm Sci Global CMC	Michael Fenster
Director, Statistics	Steven Hua
Senior Director, Clinical Statistician	Leah Isakov
Director, GTS Bio manufacturing	Carol Kirchhoff
Director, Development Strategy & Operations	Joe McClellan
VP, Clinical Pharmacology	Xu Meng
Senior Director, Clinical Research	Muhammad Iftikharur Rehman
Associate Director, Statistics	Andrew Rugaiganisa
Director, WSR WRD	Robert Schaum

BACKGROUND:

Pfizer requested a BPD Type 3 meeting to discuss the adequacy of the functional, structural, and PK similarity data comparing PF-06438179 to the reference product (US-licensed Remicade) to support the “Phase 3” development plan. Previous BPD2 meetings were held July 8 and December 18, 2013.

After review of the briefing package, FDA sent preliminary responses to Pfizer’s questions in an emailed letter dated August 1, 2014. In an email dated August 4, 2014, Pfizer provided clarifications and requested discussion of FDA responses to Questions 1, 8c, 9b, 10, 11b, and 12. Pfizer’s comments or additional questions are incorporated into the body of the minutes as well as provided as an Attachment at the end of the minutes.

The content of the letter is printed below, with the sponsor’s questions from the briefing package in *italics*; FDA’s responses (meeting preliminary comments) in normal font; and Pfizer’s August 4, 2014, emailed responses also noted in *italics*. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

Pfizer noted that they plan to request a BPD Type 4 meeting late 2016 to discuss the format and content of their proposed 351(k) BLA, planned for submission in 2017.

FDA may provide further clarifications of, or refinements and/or changes to these 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 (PHS) Act.

QUESTIONS AND RESPONSES

Question 1 (CMC)

Based on the totality of the analytical similarity assessment conducted and data provided herein, Pfizer believes that the analytical similarity between infliximab-Pfizer and infliximab-US has been established to an extent that the biosimilar product can be assessed as highly similar to the reference product infliximab-US, and is sufficient to support the following:

*(a) the initiation of the proposed phase 3 study (B5371002) from a safety perspective, and
(b) the biosimilarity assessment of infliximab-Pfizer as part of the CMC requirements of a BLA under the 351(k) of the PHS Act. Does the Agency agree?*

FDA response:

From a safety perspective, the differences between PF-06438179, and US-licensed Remicade seen in the analytical similarity exercise data submitted do not preclude the initiation of the proposed comparative clinical study (B5371002).

However, at this time, you have not provided adequate data and information for FDA to make a determination of whether PF-06438179 is highly similar to US-licensed Remicade. Note that a conclusion of “biosimilarity” will be based the totality of the evidence, including analytical, nonclinical, and clinical data submitted in the BLA, and will be a review issue.

Pfizer’s 8/4/14 emailed response:

Pfizer thanks the Agency for comments agreeing to the initiation of the comparative clinical RA study B5371002.

With reference to the BLA, Pfizer intends to test PF-06438179 future process performance qualification lots, US reference product lots and EU approved product lots using the same characterization and product quality methods which we described in the BPD3 briefing document. Pfizer is proposing that the inclusion of the comparative analytical characterization of these lots will constitute the only additional analytical information presented at the BLA compared to the BPD module 3 Similarity sections.

The agency has recommended at a recent BPD2 meeting ([REDACTED])^{(b) (4)}

[REDACTED] an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. Pfizer acknowledges that this statistical approach is broadly applicable across our Biosimilar programs and intends to implement this approach in our similarity assessment for PF-06438179.

Can the Agency confirm the above proposal is sufficient to support analytical similarity at BLA? Pfizer considers this discussion to be applicable to the demonstration of analytical similarity of PF-06438179 to the reference product as well as the demonstration of the scientific bridge between the US reference product and the EU authorized product.

Discussion:

FDA clarified that it stated that Pfizer had not provided adequate data and information for FDA to make a determination of whether PF-06438179 is highly similar to US-licensed Remicade because the full analytical data package had not yet been submitted for review. FDA further clarified that the analytical data submitted

so far and the testing Pfizer proposes to conduct appears reasonable. FDA recommended that Pfizer provide a comprehensive analysis to demonstrate that PF-06438179 has the same mechanism(s) of action as US-licensed Remicade and address all mechanisms of action with relevant functional assays (not necessarily in vivo assays) as part of its scientific justification for proposed extrapolation of clinical data to other conditions of use for which Remicade is licensed (see additional discussion under question 12).

Pfizer asked whether the statistical approach for the analytical similarity assessment based on a tiered system as recommended by FDA [REDACTED] (b) (4) [REDACTED] would be broadly applicable to their other development programs. Pfizer also asked whether requesting a BPD Type 2 meeting to further discuss the statistical approach for the PF-06438179 program would be appropriate.

FDA agreed that the statistical approach recommended [REDACTED] (b) (4) [REDACTED] could be applied to the development of PF-06438179, and agreed that Pfizer should have further discussion with the FDA regarding the ranking of quality attributes and the proposed statistical testing specific to PF-06438179.

Question 2 (CMC)

Based on the totality of the analytical similarity assessment conducted, and data provided herein, Pfizer believes that the analytical data demonstrate that infliximab-US and infliximab-EU are similar to each other and supports the use of infliximab-EU as the comparator in the proposed phase 3 study (B5371002). Does the Agency agree?

FDA response:

The data submitted thus far, including the analytical similarity data and the results from the PK similarity study (Study B5371001) appear adequate to support the scientific bridge between US-licensed Remicade and EU-approved infliximab to justify the use of EU-approved infliximab as the comparator in the proposed comparative clinical study.

Pfizer's 8/4/14 emailed response:

Pfizer thanks the Agency for confirming that the data submitted so far appears adequate to justify the use of EU-approved infliximab as the comparator in the proposed comparative clinical study. Pfizer confirms that future EU comparator lots will be tested according to the analytical characterization plan in the BPD3 briefing document (Table R.3.2.8-1), and the data filed in the IND (114,828) Annual Report, concurrent with or following use in the clinic. No further discussion required.

Question 3 (CMC)

Process-related impurities are by their very nature a function of a specific manufacturing process, including the cell line chosen, cell culture media and purification processes. Since it is generally acknowledged that the manufacturing process for a biosimilar is distinct from that of the innovator product, it is unlikely that infliximab-Pfizer will match the innovator product in process-related impurities. Pfizer's experience with the platform cell line and platform purification process used for infliximab-Pfizer, has demonstrated an appropriate safety profile for Phase 3 and commercial products. Pfizer proposes a risk based approach, guided primarily

by in depth analysis of the proposed biosimilar product's process related impurity profile against well established safety limits for process-related impurities that ensures patient safety is maintained. Does the Agency agree with the rationale and approach outlined in the briefing document?

FDA response:

Please refer to the June 21, 2014 meeting minutes (b) (4) regarding Pfizer's approach to process-related impurities. As captured in the meeting minutes, FDA advised that "we consider the advice provided herein (b) (4) regarding your approach to assessing process-related impurities in the context of biosimilar development to be applicable to your other biosimilar development programs (b) (4)

Pfizer's 8/4/14 emailed response:

Pfizer confirms that the approach to assessing process-related impurities outlined in the context of (b) (4) will be applicable to PF-06438179. No further discussion required.

Question 4 (Non-Clinical)

Does the Agency agree that the in vivo nonclinical program for infliximab-Pfizer is sufficient to support its registration as a biosimilar to the US-licensed Remicade?

FDA response:

Yes, your in vivo nonclinical program appears to be acceptable. However, the final decision regarding acceptability of the data will be a review issue.

Pfizer's 8/4/14 emailed response:

No further discussion required.

Question 5 (Clinical Pharmacology)

The sponsor believes that the pharmacokinetic similarity data from the clinical Phase 1 Study B5371001 provides sufficient and strong support for the Phase 3 biosimilarity assessment of infliximab-Pfizer, and that the pharmacokinetic similarity data package supplemented with additional population pharmacokinetic assessment in the target patient population proposed for Study B5371002 will be sufficient to fulfill the infliximab-Pfizer pharmacokinetic characterization requirement for a BLA under the 351(k) of the PHS Act. Does the Agency agree?

FDA response:

Based on the data provided, we agree that it appears that PK similarity between PF-06438179, US-licensed Remicade, and EU-approved infliximab appears to have been demonstrated. However, a final determination of PK similarity will be a review issue pending review of the data in your 351(k) application. A population PK assessment is not needed to support PK similarity; therefore, the inclusion of exploratory analysis with your proposed population PK assessment in Study B5371002 is at your discretion.

Pfizer's 8/4/14 emailed response:
No further discussion required.

Question 6 (Clinical Pharmacology/Clinical)

Does the Agency agree that the results of the Phase 1, 3-arm pharmacokinetic study, as well as the totality of analytical and physiochemical data available at the time of market application, is adequate to meet the requirement for bridging between EU-approved infliximab and the US-licensed product for the purpose of providing a scientific justification for use of EU-approved infliximab as the comparator in the planned global Phase 3 efficacy and safety study?

FDA response:
Refer to our response to Question 2.

Pfizer's 8/4/14 emailed response:
No further discussion required.

Question 7 (Clinical)

Does the Agency agree that the design of the proposed Study B5371002 (including eligibility criteria specified in the protocol) and ACR20 response at week 14 as the primary endpoint are appropriate to show no clinically meaningful differences between infliximab- Pfizer and infliximab-EU?

FDA response:
In principle, your proposed study design appears reasonable, including the primary endpoint (ACR20 response at Week 14) and entry criteria, which includes:

- Enrollment of patients with a diagnosis of rheumatoid arthritis (RA) as per the 2010 ACR/EULAR classification criteria for at least 4 months duration,
- Moderate to severe disease activity (defined as ≥ 6 tender and 6 swollen joints),
- Stable doses of methotrexate (ranging from 10-25 mg/week that may go lower due to country specific dosing requirements) and on concomitant stable doses of sulfasalazine and/or antimalarials, and
- Patients who may have received up to 2 doses of one biologic therapy for RA such as anakinra, abatacept, or anti-TNF therapies other than infliximab for which they have undergone a washout period of at least 3 months or 5 half-lives (whichever is longer) prior to the first dose of the study drug.

However, the 24-week Treatment Period 3 of your proposed study is unnecessary to support licensure of PF-06438179 in the US.

Pfizer's 8/4/14 emailed response:
No further discussion required.

Question 8 (Clinical)

a) Does the Agency agree with the proposal to allow a single dose escalation after the primary efficacy endpoint for those patients who do not respond or lose response to therapy in Study B5371002?

FDA response:

The proposal to permit dose escalation after Week 14 is at your discretion. In the event that different proportions of patients receive escalated doses in the two treatment arms, we recommend that you address the potential impact of imbalanced dose escalation on the assessment of efficacy, safety, and immunogenicity at later time points.

Pfizer's 8/4/14 emailed response:

No further discussion required.

b) Does the Agency agree with the proposal for investigators to discontinue study treatment for subjects who fail to show improvement after dose escalation?

FDA response:

We agree with your proposal to discontinue study treatment for patients who fail to demonstrate improvement after dose escalation. Refer to FDA's response to Question 8c regarding follow up of patients who discontinue study treatment.

Pfizer's 8/4/14 emailed response:

No further discussion required.

*c) Does the Agency agree with Pfizer's plan to [REDACTED] (b) (4)
[REDACTED]
[REDACTED] (unless the subject withdraws consent and/or starts participation in another trial)?*

FDA response:

To prevent missing data in key analyses, all randomized patients, even those who prematurely discontinue the randomized therapy or deviate from the protocol, should continue to return for all visits to assess safety and efficacy through the end of the double-blind period (Week 30). See FDA's response to Question 10 for further discussion.

Following subjects who discontinue study treatment between Week 30 and Week 54 of Study B5371002 for any reason other than withdrawal of consent or participation in another study via a scheduled phone call to assess safety is reasonable.

Pfizer's 8/4/14 emailed response:

Pfizer recognizes the importance of minimizing missing data for key analyses. Therefore, protocol B5371002 will be amended to reflect that subjects, who withdraw from or discontinue study treatment before Week 30 visit, will be required to return for all remaining study visits in treatment period 1 (including Week 30 visit), unless they withdraw consent to participate in the study.

*As a matter of clarification, the protocol currently requires [REDACTED] (b) (4)
[REDACTED]
[REDACTED]. Pfizer plans to amend the protocol to remove [REDACTED] (b) (4)
and instead leave the decision to have subjects withdrawn from study
treatment at the discretion of investigators.*

Discussion:

FDA responded that Pfizer's proposal seemed reasonable.

Question 9 (Clinical / Statistics)

a) Based on the discussion between Agency and Pfizer at the Biosimilar BPD Type-2 meeting on 18 December, 2013, Pfizer would like to change the metric from the previously proposed ratio of the two treatment groups to difference (infliximab- Pfizer vs. infliximab-EU) for the analysis of ACR20 response rate. Does the Agency agree with Pfizer's proposal to utilize the difference in ACR20 response rates (infliximab-Pfizer vs infliximab-EU) as the metric for the analysis of this parameter, as the basis for equivalence margin calculation and the demonstration of no clinically meaningful difference in therapeutic effect between the two products?

FDA response:

This is acceptable.

Pfizer's 8/4/14 emailed response:

No further discussion required.

b) Does the Agency agree with the methodology used for derivation of the proposed equivalence margin based on the difference in ACR20 response rates between the two treatment groups?

FDA response:

The general approach to design the comparative clinical study to, at a minimum, rule out a loss of at least 50% of the effect of the reference product, is reasonable. However, we believe that the Schiff 2008 study (ATTEST) is a relevant, adequate, and well-controlled clinical trial that should be included in the meta-analysis of historical data to estimate the treatment effect. In addition, if the primary endpoint is assessed at Week 14, the estimated effect from the Maini 1999 study (ATTRACT) used in the meta-analysis should be based on Week 14 rather than Week 30 data. Results over time are available in the literature and in the publicly available FDA Medical Review (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107726.pdf>). Because the estimated treatment effects were larger at Week 22 and Week 30 (compared to Week 14), you may want to consider evaluating the primary endpoint at one of these later time points instead.

Pfizer's 8/4/14 emailed response:

Pfizer acknowledges the Agency's view that all 5 historical randomized placebo controlled trials are relevant. Based on Agency's feedback, Pfizer would like to obtain Agency concordance with the following method of establishing the equivalence margin.

- Use of all 5 historical studies
- Use of **Week-14** ACR20 data from Maini study (FDA medical review document)
- (b) (4)
- Use 90% 2-sided CI for the difference in ACR20 response rates at Week 14 for B5371002 ((b) (4)) to conclude equivalence

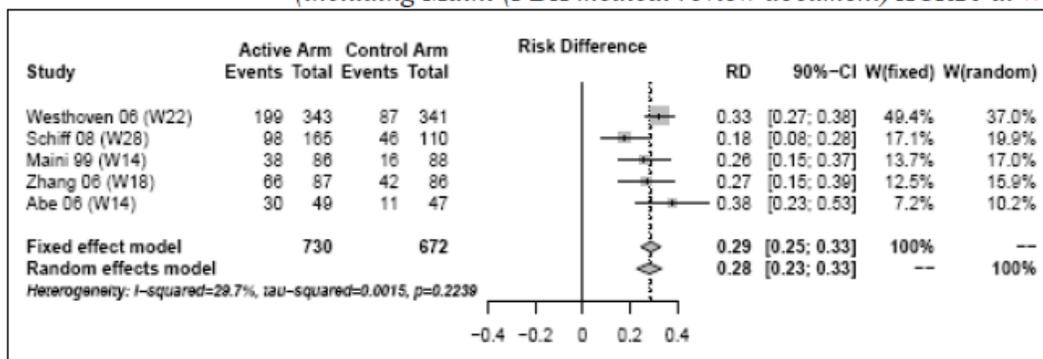
Based on the above parameters, Pfizer now proposes a 12% equivalence margin. If the Agency agrees with this proposed margin, the power of the study will be approximately 83% if the current sample size is maintained at 614.

Table 1. Margin for ACR20 based on the 5 historical studies as shown in Table 1

5 studies and ACR20 timepoint					50% of lower bound (Random effect)
Westhoven 99	Schiff 08	Zhang 06	Abe 06	Maini 99	2-sided 90% CI
Week 22	Week 28	Week 18	Week 14	Week 30	+/-12%
				Week 22	+/-12%
				Week 14	+/- 11.5%

Figure 1. Forest plot of the 5 infliximab trials

(including Maini (FDA medical review document) ACR20 at *Week 14*)



Discussion:

FDA provided the following responses to Pfizer's revised proposal for the approach to establish the equivalence margin:

- FDA agrees with use of all 5 historical studies,

- Use of week 14 for ACR20 data is acceptable,
- FDA recommends the use of a 95% 2-sided confidence interval for estimation of the effect of the infliximab over placebo using historical data and preservation of 50% of the lower bound of that confidence interval,
- The use of a 90% 2-sided confidence interval for the difference between treatment groups in ACR20 response rates in the proposed comparative clinical study is acceptable.

Pfizer inquired and FDA agreed that it is acceptable to use conventional rounding methods (to the nearest whole number) to define the equivalence margin based on the results of the meta-analysis.

c) Does the Agency agree that it is adequate to conclude equivalence, if the 95% 2-sided CI for the observed treatment difference in week 14 ACR20 response rates falls within the proposed equivalence margin of (- [REDACTED]^{(b) (4)}%) in the proposed phase 3 RA trial?

FDA response:

No, we do not agree with the proposed margin. See the response to Question 9b.

We also note that for the comparative clinical study, FDA generally expects the Type I error rate of a test of similarity to be controlled at 5%. This test could be implemented according to a Two One-Sided Tests (TOST) procedure or a confidence interval approach, in which the null hypothesis is rejected if the 90% CI for the difference between the reference product and the proposed biosimilar product falls completely within the range defined by the similarity margins.

Pfizer's 8/4/14 emailed response:

See Pfizer response to question 9b above.

d) With the proposed equivalence margin, a total sample size of approximately $N = 614$ subjects (307 subjects per arm) will have at least 85% power to demonstrate equivalence using a 2-sided 95% CI. Does the Agency agree that the proposed sample size is adequate for the proposed Phase 3 trial?

FDA response:

We defer any comments on the proposed sample size until there is agreement on the similarity margin.

Pfizer's 8/4/14 emailed response:

No further discussion required.

Question 10 (Clinical / Statistics)

Does the Agency agree with these proposed missing data handling methods for the analyses of the efficacy data for ACR (ACR20, ACR50 and ACR70) and continuous measures (e.g., [REDACTED]^{(b) (4)}) in this study?

FDA response:

The approach to consider patients who discontinue treatment early to be non-responders in analyses of ACR response endpoints is acceptable. However, the proposed analyses of continuous efficacy measures are problematic. As recommended in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, you should explicitly define the causal estimand of interest that is being targeted by each analysis, and should justify that it can be estimated with minimal and reasonable assumptions. The proposed approach (b) (4)

likely would not provide reliable estimates of the intent-to-treat estimand (i.e., the difference in mean change from baseline in some continuous efficacy endpoint at 14 weeks in all randomized patients, regardless of adherence to treatment or to the protocol) that would be an important part of the evaluation of the comparative clinical study data for your proposed biosimilar. To provide for this estimand, even patients who prematurely discontinue the randomized therapy, or deviate from the protocol, should continue to be followed for safety and efficacy assessments through the end of the double-blind period so that there should be very little missing data in intent-to-treat analyses. Additional per-protocol analyses should be pre-specified (e.g., based only on the subset of patients who complete the study and adhere to the protocol).

Pfizer's 8/4/14 emailed response:

Pfizer would like to further discuss the Agency's recommendations.

Discussion:

Pfizer asked if FDA has a preferred method to handle missing data.

FDA's recommendation at this time is that patients who prematurely discontinue study treatment should still continue to be followed and all data for such a subject should be collected as it would have been otherwise. This would provide for a "retrieved drop-out" type analysis utilizing all observed data. FDA encouraged Pfizer to submit proposals for the best approach to handle missing data in the context of their protocol.

Pfizer agreed that it is important to avoid bias in addressing these issues and stated that they will continue to work with the Agency to reach agreement. They stated their plan to start the study in about a month.

FDA and Pfizer agreed that determination of the best methods to address this issue should be reached (and documented) before unblinding of the study.

Question 11 (Clinical/Clinical Pharmacology/CMC)

Does the Agency agree with the following aspects of the immunogenicity assessment strategy for the proposed Phase 3 study B5371002:

a) The overall design for the comparative assessment of immunogenicity between infliximab-Pfizer and infliximab-EU, including the frequency and duration of sampling and the comparative 12 month assessment for ADA and neutralizing antibodies?

FDA response:

The proposed comparative assessment of immunogenicity, including the frequency and duration of sampling for ADA and neutralizing antibodies, appears reasonable. The final acceptance of the data will be a review issue.

Pfizer's 8/4/14 emailed response:

No further discussion required.

b) The proposed plan for sample analysis?

FDA response:

All samples that are tested should be tested with both versions of the assays to ensure the completeness of a direct comparison of immunogenicity.

Pfizer's 8/4/14 emailed response:

Pfizer acknowledges that during the December 18th BPD2 meeting the FDA recommended testing samples from all patients treated with the proposed biosimilar or comparator product with one assay that uses the biosimilar molecular as the capture and/or detecting reagent. While Pfizer's strategy thus far has focused on a two-assay approach to immunogenicity testing, Pfizer is now re-evaluating the option of using one assay as initially recommended.

Discussion:

FDA confirmed that the use of one assay for immunogenicity testing as initially recommended is still applicable, and therefore Pfizer's proposed plan is acceptable.

c) Does the Agency agree that the proposed plan for evaluating the effect of switching from infliximab-EU to infliximab-Pfizer would have sufficiently meaningful data to assess the immunogenicity of infliximab-Pfizer in comparison to infliximab-EU in the planned Phase 3 study (B5371002)?

FDA response:

We agree that the proposed plan of a single transition from EU-approved infliximab to PF-06438179 is reasonable to evaluate the safety and immunogenicity in patients and to descriptively compare the findings between the 2 groups.

Pfizer's 8/4/14 emailed response:

No further discussion required.

Question 12 (Clinical/Regulatory)

Does the FDA agree that based on the analytical and non-clinical data that Pfizer has provided, including primary sequence, charge heterogeneity, purity, higher order structure, aggregation, multiple levels of biologic activity data (as explained in the Company Position below), as well as findings from a single dose TK/tolerability in rats, and favorable clinical PK results from study B5371001, that a 2-arm, randomized, double-blind, parallel-group clinical study in RA (with a

single transition), would be adequate to support a demonstration of no clinically meaningful differences between infliximab-Pfizer and infliximab-EU and extrapolation to all licensed indications for infliximab?

FDA response:

The analytical, nonclinical, and pharmacokinetic data provided appear to support the development of PF-06438179 as a proposed biosimilar to US-licensed Remicade. If agreement can be reached on aspects of the comparative clinical study design in patients with RA discussed in FDA's responses to Questions 8, 9 and 10 above, the data may be sufficient to support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade. However, the adequacy of the data will be a review issue. As discussed at our previous meeting for this product on December 18, 2013, you will need to provide a sufficient scientific justification for extrapolating clinical data to support the determination of biosimilarity for each condition of use for which you seek licensure. The adequacy of this justification will be a review issue.

Pfizer's 8/4/14 emailed response:

With respect to the scientific justification required for extrapolation from rheumatoid arthritis to each condition of use of marketed infliximab, Pfizer proposes to group these into two major areas of commonality: 1) arthropathies (ankylosing spondylitis, psoriatic arthritis) and psoriasis, and 2) inflammatory bowel diseases (Crohn's disease and ulcerative colitis).

Discussion:

Pfizer asked if FDA recommended specific analyses to support extrapolation from rheumatoid arthritis to other conditions of use.

FDA stated that while they could not provide a list of recommended analyses, Pfizer should perform a comprehensive analysis, including functional assays specific to the indications for which the reference product is approved and for which Pfizer seeks licensure for PF-06438179, e.g., Crohn's disease or psoriasis. FDA clarified that even if Pfizer chose to group the diseases based on commonality, Pfizer would need to specifically and separately address each condition of use for which licensure is sought, noting which data were supporting extrapolation for each condition of use. Pfizer should also provide adequate justification for extrapolation to each condition of use where extrapolation is proposed.

PREA PEDIATRIC STUDY PLAN

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, 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. 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:

Pfizer acknowledged the need to address PREA, and asked if there was a specific iPSP template for biosimilars.

FDA indicated that the template used for iPSPs for proposed biosimilar products is the same as that for standalone products; however, the content may differ. FDA explained that each indication for which Pfizer is seeking licensure would need to be addressed (separately). Pfizer should consider, among other things, what is known about use of the reference product in the pediatric population to determine how to adequately address PREA for its proposed product, including whether a justification for extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) could be provided in the context of its biosimilar development program.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 [CDER/CBER Position on Use of SI Units for Lab Tests](#).

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS:

Pfizer's August 4, 2014, emailed responses to FDA's meeting preliminary comments.

Additional Clarifications for 5 Aug BPD3 meeting for Infliximab-Pfizer (PF-06438179)

Pfizer's questions in *italics font* are followed by the Agency's responses in normal font. Pfizer's Clarifications follow FDA comments in italics.

Question 1 (CMC)

Based on the totality of the analytical similarity assessment conducted and data provided herein, Pfizer believes that the analytical similarity between infliximab-Pfizer and infliximab-US has been established to an extent that the biosimilar product can be assessed as highly similar to the reference product infliximab-US, and is sufficient to support the following:

*(a) the initiation of the proposed phase 3 study (B5371002) from a safety perspective, and
(b) the biosimilarity assessment of infliximab-Pfizer as part of the CMC requirements of a BLA under the 351(k) of the PHS Act. Does the Agency agree?*

FDA response:

From a safety perspective, the differences between PF-06438179, and US-licensed Remicade seen in the analytical similarity exercise data submitted do not preclude the initiation of the proposed comparative clinical study (B5371002).

However, at this time, you have not provided adequate data and information for FDA to make a determination of whether PF-06438179 is highly similar to US-licensed Remicade. Note that a conclusion of "biosimilarity" will be based the totality of the evidence, including analytical, nonclinical, and clinical data submitted in the BLA, and will be a review issue.

Pfizer Response

Pfizer thanks the Agency for comments agreeing to the initiation of the comparative clinical RA study B5371002.

With reference to the BLA, Pfizer intends to test PF-06438179 future process performance qualification lots, US reference product lots and EU approved product lots using the same characterization and product quality methods which we described in the BPD3 briefing document. Pfizer is proposing that the inclusion of the comparative analytical characterization of these lots will constitute the only additional analytical information presented at the BLA compared to the BPD module 3 Similarity sections.

The agency has recommended at a recent BPD2 meeting [REDACTED] (b) (4) [REDACTED] an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. Pfizer acknowledges that this statistical approach is broadly applicable across our Biosimilar programs and intends to implement this approach in our similarity assessment for PF-06438179.

Can the Agency confirm the above proposal is sufficient to support analytical similarity at BLA? Pfizer considers this discussion to be applicable to the demonstration of analytical similarity of PF-06438179 to the reference product as well as the demonstration of the scientific bridge between the US reference product and the EU authorized product.

Question 2 (CMC)

Based on the totality of the analytical similarity assessment conducted, and data provided herein, Pfizer believes that the analytical data demonstrate that infliximab-US and infliximab-EU are similar to each other and supports the use of infliximab-EU as the comparator in the proposed phase 3 study (B5371002). Does the Agency agree?

FDA response:

The data submitted thus far, including the analytical similarity data and the results from the PK similarity study (Study B5371001) appear adequate to support the scientific bridge between US-licensed Remicade and EU-approved infliximab to justify the use of EU-approved infliximab as the comparator in the proposed comparative clinical study.

Pfizer Response

Pfizer thanks the Agency for confirming that the data submitted so far appears adequate to justify the use of EU-approved infliximab as the comparator in the proposed comparative clinical study. Pfizer confirms that future EU comparator lots will be tested according to the analytical characterization plan in the BPD3 briefing document (Table R.3.2.8-1), and the data filed in the IND (114,828) Annual Report, concurrent with or following use in the clinic.

No further discussion required.

Question 3 (CMC)

Process-related impurities are by their very nature a function of a specific manufacturing process, including the cell line chosen, cell culture media and purification processes. Since it is generally acknowledged that the manufacturing process for a biosimilar is distinct from that of the innovator product, it is unlikely that infliximab-Pfizer will match the innovator product in process-related impurities. Pfizer's experience with the platform cell line and platform purification process used for infliximab-Pfizer, has demonstrated an appropriate safety profile for Phase 3 and commercial products. Pfizer proposes a risk based approach, guided primarily by in depth analysis of the proposed biosimilar product's process related impurity profile against well-established safety limits for process-related impurities that ensures patient safety is maintained. Does the Agency agree with the rationale and approach outlined in the briefing document?

FDA response:

Please refer to the June 21, 2014 meeting minutes (b) (4) regarding Pfizer's approach to process-related impurities. As captured in the meeting minutes, FDA advised that "we consider the advice provided herein (b) (4) regarding your approach to assessing process-related impurities in the context of biosimilar development to be applicable to your other biosimilar development programs (b) (4)

Pfizer response

Pfizer confirms that the approach to assessing process-related impurities outlined in the context of (b) (4) will be applicable to PF-06438179.

No further discussion required.

Question 4 (Non-Clinical)

Does the Agency agree that the in vivo nonclinical program for infliximab-Pfizer is sufficient to support its registration as a biosimilar to the US-licensed Remicade?

FDA response:

Yes, your in vivo nonclinical program appears to be acceptable. However, the final decision regarding acceptability of the data will be a review issue.

Pfizer response

No further discussion required.

Question 5 (Clinical Pharmacology)

The sponsor believes that the pharmacokinetic similarity data from the clinical Phase 1 Study B5371001 provides sufficient and strong support for the Phase 3 biosimilarity assessment of infliximab-Pfizer, and that the pharmacokinetic similarity data package supplemented with additional population pharmacokinetic assessment in the target patient population proposed for Study B5371002 will be sufficient to fulfill the infliximab-Pfizer pharmacokinetic characterization requirement for a BLA under the 351(k) of the PHS Act. Does the Agency agree?

FDA response:

Based on the data provided, we agree that it appears that PK similarity between PF-06438179, US-licensed Remicade, and EU-approved infliximab appears to have been demonstrated. However, a final determination of PK similarity will be a review issue pending review of the data in your 351(k) application. A population PK assessment is not needed to support PK similarity; therefore, the inclusion of exploratory analysis with your proposed population PK assessment in Study B5371002 is at your discretion.

Pfizer response

No further discussion required.

Question 6 (Clinical Pharmacology/Clinical)

Does the Agency agree that the results of the Phase 1, 3-arm pharmacokinetic study, as well as the totality of analytical and physiochemical data available at the time of market application, is adequate to meet the requirement for bridging between EU-approved infliximab and the US-licensed product for the purpose of providing a scientific justification for use of EU-approved infliximab as the comparator in the planned global Phase 3 efficacy and safety study?

FDA response:

Refer to our response to Question 2.

Pfizer response

No further discussion required.

Question 7 (Clinical)

Does the Agency agree that the design of the proposed Study B5371002 (including eligibility criteria specified in the protocol) and ACR20 response at week 14 as the primary endpoint are appropriate to show no clinically meaningful differences between infliximab- Pfizer and infliximab-EU?

FDA response:

In principle, your proposed study design appears reasonable, including the primary endpoint (ACR20 response at Week 14) and entry criteria, which includes:

- Enrollment of patients with a diagnosis of rheumatoid arthritis (RA) as per the 2010 ACR/EULAR classification criteria for at least 4 months duration,
- Moderate to severe disease activity (defined as ≥ 6 tender and 6 swollen joints),
- Stable doses of methotrexate (ranging from 10-25 mg/week that may go lower due to country specific dosing requirements) and on concomitant stable doses of sulfasalazine and/or antimalarials, and
- Patients who may have received up to 2 doses of one biologic therapy for RA such as anakinra, abatacept, or anti-TNF therapies other than infliximab for which they have undergone a washout period of at least 3 months or 5 half-lives (whichever is longer) prior to the first dose of the study drug.

However, the 24-week Treatment Period 3 of your proposed study is unnecessary to support licensure of PF-06438179 in the US.

Pfizer response

No further discussion required.

Question 8 (Clinical)

a) Does the Agency agree with the proposal to allow a single dose escalation after the primary efficacy endpoint for those patients who do not respond or lose response to therapy in Study B5371002?

FDA response:

The proposal to permit dose escalation after Week 14 is at your discretion. In the event that different proportions of patients receive escalated doses in the two treatment arms, we recommend that you address the potential impact of imbalanced dose escalation on the assessment of efficacy, safety, and immunogenicity at later time points.

Pfizer response

No further discussion required.

b) Does the Agency agree with the proposal for investigators to discontinue study treatment for subjects who fail to show improvement after dose escalation?

FDA response:

We agree with your proposal to discontinue study treatment for patients who fail to

demonstrate improvement after dose escalation. Refer to FDA's response to Question 8c regarding follow up of patients who discontinue study treatment.

Pfizer response

No further discussion required.

c) Does the Agency agree with Pfizer's plan to [REDACTED] (b) (4) [REDACTED] unless the subject withdraws consent and/or starts participation in another trial)?

FDA response:

To prevent missing data in key analyses, all randomized patients, even those who prematurely discontinue the randomized therapy or deviate from the protocol, should continue to return for all visits to assess safety and efficacy through the end of the double-blind period (Week 30). See FDA's response to Question 10 for further discussion.

Following subjects who discontinue study treatment between Week 30 and Week 54 of Study B5371002 for any reason other than withdrawal of consent or participation in another study via a scheduled phone call to assess safety is reasonable.

Pfizer response

Pfizer recognizes the importance of minimizing missing data for key analyses. Therefore, protocol B5371002 will be amended to reflect that subjects, who withdraw from or discontinue study treatment before Week 30 visit, will be required to return for all remaining study visits in treatment period 1 (including Week 30 visit), unless they withdraw consent to participate in the study.

As a matter of clarification, the protocol currently requires [REDACTED] (b) (4)

[REDACTED] Pfizer plans to amend the protocol to remove [REDACTED] (b) (4) and instead leave the decision to have subjects withdrawn from study treatment at the discretion of investigators.

Question 9 (Clinical / Statistics)

a) Based on the discussion between Agency and Pfizer at the Biosimilar BPD Type-2 meeting on 18 December, 2013, Pfizer would like to change the metric from the previously proposed ratio of the two treatment groups to difference (infliximab- Pfizer vs. infliximab-EU) for the analysis of ACR20 response rate. Does the Agency agree with Pfizer's proposal to utilize the difference in ACR20 response rates (infliximab-Pfizer vs infliximab-EU) as the metric for the analysis of this parameter, as the basis for equivalence margin calculation and the demonstration of no clinically meaningful difference in therapeutic effect between the two products?

FDA response:

This is acceptable.

Pfizer response

No further discussion required.

b) Does the Agency agree with the methodology used for derivation of the proposed equivalence margin based on the difference in ACR20 response rates between the two treatment groups?

FDA response:

The general approach to design the comparative clinical study to, at a minimum, rule out a loss of at least 50% of the effect of the reference product, is reasonable. However, we believe that the Schiff 2008 study (ATTEST) is a relevant, adequate, and well-controlled clinical trial that should be included in the meta-analysis of historical data to estimate the treatment effect. In addition, if the primary endpoint is assessed at Week 14, the estimated effect from the Maini 1999 study (ATTRACT) used in the meta-analysis should be based on Week 14 rather than Week 30 data. Results over time are available in the literature and in the publicly available FDA Medical Review (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107726.pdf>). Because the estimated treatment effects were larger at Week 22 and Week 30 (compared to Week 14), you may want to consider evaluating the primary endpoint at one of these later time points instead.

Pfizer response

Pfizer acknowledges the Agency's view that all 5 historical randomized placebo controlled trials are relevant. Based on Agency's feedback, Pfizer would like to obtain Agency concordance with the following method of establishing the equivalence margin.

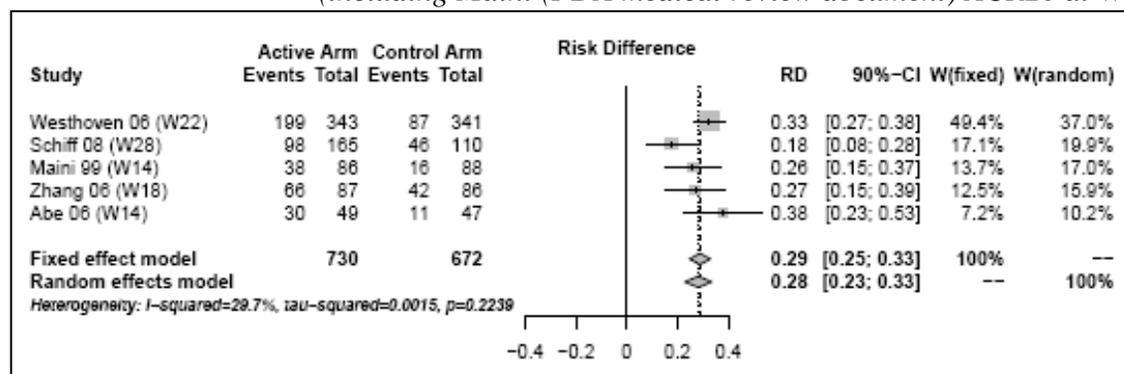
- *Use of all 5 historical studies*
- *Use of **Week-14** ACR20 data from Maini study (FDA medical review document)*
- *[REDACTED] (b) (4)*
- *Use 90% 2-sided CI for the difference in ACR20 response rates at Week 14 for B5371002 [REDACTED] (b) (4) to conclude equivalence*

Based on the above parameters, Pfizer now proposes a 12% equivalence margin. If the Agency agrees with this proposed margin, the power of the study will be approximately 83% if the current sample size is maintained at 614.

Table 1. Margin for ACR20 based on the 5 historical studies as shown in Table 1

5 studies and ACR20 timepoint					50% of lower bound (Random effect)
Westhoven 99	Schiff 08	Zhang 06	Abe 06	Maini 99	2-sided 90% CI
Week 22	Week 28	Week 18	Week 14	Week 30	+/-12%
				Week 22	+/-12%
				Week 14	+/-11.5%

Figure 1. Forest plot of the 5 infliximab trials (including Maini (FDA medical review document) ACR20 at Week 14)



Does the Agency agree that it is adequate to conclude equivalence, if the 95% 2-sided CI for the observed treatment difference in week 14 ACR20 response rates falls within the proposed equivalence margin of (- (b) (4) %) in the proposed phase 3 RA trial?

FDA response:

No, we do not agree with the proposed margin. See the response to Question 9b.

We also note that for the comparative clinical study, FDA generally expects the Type I error rate of a test of similarity to be controlled at 5%. This test could be implemented according to a Two One-Sided Tests (TOST) procedure or a confidence interval approach, in which the null hypothesis is rejected if the 90% CI for the difference between the reference product and the proposed biosimilar product falls completely within the range defined by the similarity margins.

Pfizer response

See Pfizer response to question 9b above.

c) With the proposed equivalence margin, a total sample size of approximately N = 614 subjects (307 subjects per arm) will have at least 85% power to demonstrate equivalence using a 2-sided

95% CI. Does the Agency agree that the proposed sample size is adequate for the proposed Phase 3 trial?

FDA response:

We defer any comments on the proposed sample size until there is agreement on the similarity margin.

Pfizer response

No further discussion required.

Question 10 (Clinical / Statistics)

Does the Agency agree with these proposed missing data handling methods for the analyses of the efficacy data for ACR (ACR20, ACR50 and ACR70) and continuous measures (e.g., (b) (4) in this study?

FDA response:

The approach to consider patients who discontinue treatment early to be non-responders in analyses of ACR response endpoints is acceptable. However, the proposed analyses of continuous efficacy measures are problematic. As recommended in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, you should explicitly define the causal estimand of interest that is being targeted by each analysis, and should justify that it can be estimated with minimal and reasonable assumptions. The proposed approach (b) (4)

likely would not provide reliable estimates of the intent-to-treat estimand (i.e., the difference in mean change from baseline in some continuous efficacy endpoint at 14 weeks in all randomized patients, regardless of adherence to treatment or to the protocol) that would be an important part of the evaluation of the comparative clinical study data for your proposed biosimilar. To provide for this estimand, even patients who prematurely discontinue the randomized therapy, or deviate from the protocol, should continue to be followed for safety and efficacy assessments through the end of the double-blind period so that there should be very little missing data in intent-to-treat analyses. Additional per-protocol analyses should be pre-specified (e.g., based only on the subset of patients who complete the study and adhere to the protocol).

Pfizer response

Pfizer would like to further discuss the Agency's recommendations.

Question 11 (Clinical/Clinical Pharmacology/CMC)

Does the Agency agree with the following aspects of the immunogenicity assessment strategy for the proposed Phase 3 study B5371002:

a) The overall design for the comparative assessment of immunogenicity between infliximab-Pfizer and infliximab-EU, including the frequency and duration of sampling and the comparative 12 month assessment for ADA and neutralizing antibodies?

FDA response:

The proposed comparative assessment of immunogenicity, including the frequency and

duration of sampling for ADA and neutralizing antibodies, appears reasonable. The final acceptance of the data will be a review issue.

Pfizer Response:

No further discussion required.

b) *The proposed plan for sample analysis?*

FDA response:

All samples that are tested should be tested with both versions of the assays to ensure the completeness of a direct comparison of immunogenicity.

Pfizer Response:

Pfizer acknowledges that during the December 18th BPD2 meeting the FDA recommended testing samples from all patients treated with the proposed biosimilar or comparator product with one assay that uses the biosimilar molecular as the capture and/or detecting reagent. While Pfizer's strategy thus far has focused on a two-assay approach to immunogenicity testing, Pfizer is now re-evaluating the option of using one assay as initially recommended.

c) *Does the Agency agree that the proposed plan for evaluating the effect of switching from infliximab-EU to infliximab-Pfizer would have sufficiently meaningful data to assess the immunogenicity of infliximab-Pfizer in comparison to infliximab-EU in the planned Phase 3 study (B5371002)?*

FDA response:

We agree that the proposed plan of a single transition from EU-approved infliximab to PF-06438179 is reasonable to evaluate the safety and immunogenicity in patients and to descriptively compare the findings between the 2 groups.

Pfizer Response:

No further discussion required.

Question 12 (Clinical/Regulatory)

Does the FDA agree that based on the analytical and non-clinical data that Pfizer has provided, including primary sequence, charge heterogeneity, purity, higher order structure, aggregation, multiple levels of biologic activity data (as explained in the Company Position below), as well as findings from a single dose TK/tolerability in rats, and favorable clinical PK results from study B5371001, that a 2-arm, randomized, double-blind, parallel-group clinical study in RA (with a single transition), would be adequate to support a demonstration of no clinically meaningful differences between infliximab-Pfizer and infliximab-EU and extrapolation to all licensed indications for infliximab?

FDA response:

The analytical, nonclinical, and pharmacokinetic data provided appear to support the development of PF-06438179 as a proposed biosimilar to US-licensed Remicade. If agreement can be reached on aspects of the comparative clinical study design in patients with RA discussed in FDA's responses to Questions 8, 9 and 10 above, the data may be sufficient to support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade. However, the adequacy of the data will be a review issue. As discussed at our previous meeting for this product on December 18,

2013, you will need to provide a sufficient scientific justification for extrapolating clinical data to support the determination of biosimilarity for each condition of use for which you seek licensure. The adequacy of this justification will be a review issue.

Pfizer Response:

With respect to the scientific justification required for extrapolation from rheumatoid arthritis to each condition of use of marketed infliximab, Pfizer proposes to group these into two major areas of commonality: 1) arthropathies (ankylosing spondylitis, psoriatic arthritis) and psoriasis, and 2) inflammatory bowel diseases (Crohn's disease and ulcerative colitis).

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/s/

CHRISTINE H CHUNG
09/04/2014