CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761103Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110426

MEETING MINUTES

Pfizer Inc
Attention: Christine Kobryn, PhD
Director Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Kobryn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-05280586.

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2018. The purpose of the meeting was to discuss the format and content of a Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act).

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

If you have any questions, call Thomas Iype, Regulatory Project Manager at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: March 8, 2018; 2:00 p.m. – 3:00 p.m. (EST)
Meeting Location: Teleconference

Application Number: IND 110426
Product Name: PF-05280586
Proposed Indications: The same indications approved for US-licensed Rituxan.
Sponsor/Applicant Name: Pfizer Inc

Meeting Chair: Yvette Kasamon, MD
Meeting Recorder: Thomas Iype, PharmD, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products:
R. Angelo de Claro, MD, *Acting Deputy Division Director*
Yvette Kasamon, MD, *Acting Clinical Team Leader*
Alexandria Schwarsin, MD, *Clinical Reviewe*r

Office of Drug Evaluation II/Division of Pulmonary, Allergy, and Rheumatology Products
Nikolay Nikolov, MD, *Clinical Team Leader*
Suzette Peng, MD, *Clinical Reviewer*

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, *Supervisory, Pharmacologist/Toxicologist*

Office of Clinical Pharmacology (OCP)/Immediate Office
Sarah Schrieber, PharmD, *Clinical Pharmacology Reviewer*

OCP/Division of Clinical Pharmacology II
Ping Ji, *Clinical Pharmacology Team Leader*
Dipak Pisal, PhD, *Clinical Pharmacology Reviewer*

Office of Biostatistics
Shein-Chung Chow, PhD, Associate Director for Biosimilar Review

OB/Division of Biometrics II
Robert Abugov, PhD, *Biometrics Team Leader*
Rebecca Rothwell, MS, PhD, *Biometrics Reviewer*

OB/Division of Biometrics V
Lie Nie, PhD, *Biometrics Team Leader*

OB/Division of Biometrics VI
Meiyu Shen, PhD, *CMC Statistics Team Leader*
Chao Wang, PhD, *CMC Statistics Reviewer*

Office of Biotechnology Products
Christopher Downey, PhD, *Review Chief*
Mate Tolnay, PhD, *Biologist*
Bazarragchaa Damdinsuren, MD, PhD, *Team Leader*

Office of Process and Facilities/Division of Microbial Assessment
Aimee Cunningham, PhD, MPH, *Microbiology Reviewer*
Scott Nichols, PhD, *Microbiology Reviewer*

Office of New Drugs/Therapeutic Biologics and Biosimilars Staff
Sue Lim, MD, *Team Leader*
Stacey Ricci, MEng, ScD, *Reviewer*
Tyree Newman, *Regulatory Project Manager*

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese, *Independent Assessor*
Marc Goldstein, *Independent Assessor*

SPONSOR ATTENDEES
Julie Rosenberg, MD, *Biosimilar Development Asset Lead*
Tahira Khan, MD, MSC, *Global Clinical Lead*
Jeffery Robbins, MS, *Statistics Lead*
Nandita Mukherjee, MD, MPH, *Safety Risk Lead*
Richat Abbas, PhD, *Clinical Pharmacology Lead*
Christine Kobryn, PhD, *Global Regulatory Lead*
Sharon Bauer, BS, MBA, *US Regulatory Strategist*
Kari Leff, BS, RPh, *Global CMC Regulatory Lead*
Maureen Mullen, PhD, *Technical Project Lead*
Thomas Lerch, PhD, *Analytical Research and Development Lead*
Peter Lee, *Statistical Programming & Analysis Lead*
Vincent Amoruccio, *Statistical Programming & Analysis, Therapeutic Area Lead Biosimilars*
Rebecca Hintze, *Statistical Programming & Analysis, Therapeutic Area Lead Oncology*

1.0 BACKGROUND

On January 11, 2018, FDA received a BPD Type 4 meeting request from Pfizer Inc. The purpose of this meeting was to discuss the format and content of a Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act). PF-05280586 is a monoclonal antibody proposed to be biosimilar to US-licensed Rituxan.

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 Inc and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1: *Does the FDA have any feedback on the proposed structure and format of the 351(k) BLA for PF-05280586 as presented in Appendix 3 of the Meeting Package Materials such that it meets the FDA's expectations for e-CTD submission?*

FDA Response to Question 1: A risk management plan is required in module one.

Discussion: The Sponsor proposed that a risk evaluation and mitigation strategy (REMS) is not necessary for the drug product because there are no new safety concerns that have been identified by the Sponsor. The Sponsor suggested to provide a Medication Guide.

FDA clarified the expected content of a risk management plan. The Sponsor should outline their plans for safety surveillance and risk mitigation.

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

FDA Response to Question 2: Your "351(k) roadmap" as presented in appendix 4 in eCTD Section 1.12.11 meets the FDA's expectation for a user-friendly navigational tool.

Discussion: No discussion occurred.

Question 3: *Does FDA have additional comments on the adequacy of the proposed structure of the BLA to support the review?*

FDA Response to Question 3: Please see additional comments provided from product quality microbiology at the end of Section 2.0 (DISCUSSION).

<u>Discussion:</u> The Sponsor stated that they will include the preliminary manufacturing schedules for both the drug substance and drug product in Module 1 of the BLA. FDA noted that submission of the manufacturing schedules in Module 1 in the initial BLA submission is acceptable. FDA clarified that a manufacturing simulation of the drug product for the pre-license drug product inspection is acceptable. However, the drug substance site must be in operation manufacturing the product at the time of the pre-license drug substance inspection.

The Sponsor anticipates submitting the BLA in the end of May or beginning of June of 2018, and the scheduled harvest dates in drug substance manufacturing are October 1 and 8 of 2018.

<u>Question 4:</u> *Does FDA have any feedback with the proposed labeling concept for PF-05280586 to support the BLA submission?*

<u>FDA Response to Question 4:</u> Your proposed labeling concept is acceptable.

Discussion: No discussion occurred.

<u>Question 5:</u> *Does the Agency have any feedback on the proposal to include the final clinical study report for B3281006 as the 4-Month Safety Update?*

<u>FDA Response to Question 5:</u> For the primary endpoint we expect all patients to be followed for a minimum of 26 weeks, and for that data to be included in the original BLA submission.

<u>Discussion:</u> For study B3281006, the Sponsor stated that the clinical study report to be submitted at the time of BLA submission will include data on the primary efficacy endpoint of overall response rate (ORR) through week 26 for all study participants. The Agency requested that for the initial BLA submission, the Sponsor submit all available efficacy data for study B3281006 (including duration of response) on all patients, including past week 26 where available and including patients not yet followed through week 52. The Sponsor agreed to this request.

The Sponsor anticipates that the initial BLA submission will include data for 80% of subjects who will have completed the study through week 52 or have discontinued prior to week 52. The Sponsor will provide a final clinical study report that will include results for both the primary and secondary endpoints for all study participants as the 4-month safety and efficacy update.

<u>Question 6:</u> *In accordance with the review process entitled "The Program" in BsUFA II (effective October 2017). Pfizer will submit a comprehensive application in the original 351(k) submission (see Appendix 3 TOC) and does not anticipate submitting any minor components within 30 days after our original submission. Pfizer supports the timing of interactions and information exchange included in "The Program," and does not foresee a*

need for an alternative approach in the form of a Formal Communication Plan. Does FDA agree with our proposal and have any feedback?

FDA Response to Question 6: We agree than an alternative approach in the form of a Formal Communication Plan is not needed.

Discussion: No discussion occurred.

Question 7: *The proposed format for PF-05280586 presented in Appendix 5 has been informed by previous BPD4 engagements that the Sponsor has had with the FDA regarding the Pfizer/Hospira proposed biosimilar portfolio. 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 5?*

FDA Response to Question 7: The proposed organization of Section 3.2.R.3 seems acceptable.

Discussion: No discussion occurred.

Question 8: *Does FDA have any feedback on the proposed presentation of summary information (Appendix 5) regarding the lots of PF-05280586, rituximab-US and rituximab-EU used in the analytical biosimilarity assessment?*

FDA Response to Question 8: For each PF-05280586 drug substance lot and drug product lot, provide information on the use of the lot, corresponding drug substance or drug product lot number, manufacturing site, scale, and date. Please indicate dosage form (i.e., 100 mg/10 mL or 500 mg/50 mL) for each PF-05280586 drug product, U.S.-licensed Rituxan, and E.U.-approved MabThera lot included in the similarity assessment.

You indicate that the similarity assessment contains a total of 10 PF-05280586 drug substance lots and 12 PF-05280586 drug product lots produced at the commercial scale and 5 PF-05280586 drug substance lots at development scale. Provide scientific justification for using lots produced at both commercial and development scales in the analytical similarity assessment.

For all quality attributes measured relative to a reference standard, for example ADCC and CDC, provide information about the reference standard(s) used for each measurement in 3.2.R.3.5 Appendix-Raw Data. If more than one reference standard was used on different assay occasions for a quality attribute, you will need to provide data to support a scientific bridge between all of the reference standards used in the evaluation of that attribute. Clearly describe the relationship between the reference standards, and provide your rationale as to how the data support the bridge. In the absence of an adequate bridge, data determined using different reference standards cannot be pooled for analysis.

The number of lots for PF-05280586 compared to the number for U.S.-licensed Rituxan or E.U.-approved MabThera are highly imbalanced. For the Tier 1 equivalence test, provide an adequate adjustment for sample size imbalance in Section 3.2.R.3.1.1.

Discussion: No discussion occurred.

Question 9: *Does FDA have any feedback on the proposed locations for the analytical methods and analytical method validations as proposed above (Table 4 of Meeting Package) and in Appendix 5?*

FDA Response to Question 9: Address the following in the BLA:

- Table 4 states that the descriptions and validations for the drug product stability methods not already provided in 3.2.P.5.2 are proposed to be included in Section 3.2.P.8.3. The analytical method descriptions and method validations of all methods used in post-approval stability should be included in Sections 3.2.P.5.2 and 3.2.P.5.3.
- Additionally, for any release or stability methods transferred from the site of validation to a different site(s) for commercial testing, provide method transfer reports in 3.2.R.2.
- Qualification/validation summaries of characterization methods used in analytical biosimilarity assessment that are not already included in Sections 3.2.S.4.3 and 3.2.P.5.3 should be provided in Section 3.2.R.3.

Discussion: No discussion occurred.

Question 10: *Does FDA have any feedback regarding the drug product validation strategy for* (b) (4) *?*

FDA Response to Question 10: The validation strategy of the drug product manufacturing process for (b) (4) appears acceptable. However, if (b) (4) Adequacy of the process validation will be a review issue.

Discussion: No discussion occurred.

Question 11: *Does FDA have any feedback on the proposed placement (3.2.P.3 Manufacture) of the identified location of the cross-referenced information within the DMF?*

FDA Response to Question 11: All product-specific process validation information, including media fills and their associated environmental monitoring, and sterile hold time validation, should be included in the BLA and not in a DMF.

Discussion: No discussion occurred.

(b

Additional Statistical Comments

1. We remind you of the previous comments communicated by the FDA and meeting discussions on August 6, 2014 and May 18, 2017. We note that in Study B3281001, the ACR20/50/70 response rates of the PF-05280586 arm are numerically lower as compared to the reference product arm. You should provide justification as to why these differences support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan. Additional supportive data should include analyses of the ACR and DAS-28 components, including treatment differences and corresponding confidence intervals. Any post-hoc analyses should be adequately justified and detailed.

2. While we acknowledge that Study B3281001 and B3281004 were not designed or powered to assess efficacy endpoints, all analyses of all endpoints should be adequately described for replication by the reviewer in the statistical analysis plan. Provide all analysis details, including the handling of missing data for endpoints in addition to DAS28 and ACR20 and any post-hoc analyses, in your submission. Clearly identify how subjects who discontinue treatment but remained in the study versus subjects who dropped out of the study were handled in this design and in the analyses.

3. Provide analyses of the individual components of ACR20 and change from baseline in DAS28-CRP at week 25 in Study B3281004 and at the end of Course 1 of Study B3281004. Include the point estimates and 95% confidence intervals for the differences between treatments.

4. For study B3281006, please provide numbers and percentages of censored patients for duration of response evaluation before week 26 for overall patients and separately by treatment arms.

Discussion: The following comments pertain to the additional statistical comments 1, 3, and 4:

Item 1: **The Sponsor stated the statistical analyses planned for evaluating clinical efficacy endpoints, including ACR and DAS-28, for Study B3281001 were appropriate for the study design and study objectives. The Sponsor asked FDA to clarify the request for analyses to evaluate "treatment differences and corresponding confidence intervals" and proposed to submit the requested additional analyses, if still necessary, in response to an information request to be provided by FDA during the BLA review.**

FDA reiterated its recommendation to the Sponsor to include the requested analyses in the BLA submission, as it is the Sponsor's responsibility to justify that differences in ACR20/50/70 response rates do not preclude demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan.

Item 3: **The Sponsor suggested that the 95% confidence intervals would result in a wide range and be of limited usefulness due to the small number of study subjects (30 to 33) in the treatment groups.**

Similar to the discussion of Item 1, FDA re-iterated its recommendation to the Sponsor to include the requested analyses in the BLA submission.

Item 4: **The Sponsor stated that their understanding of FDA's request for the secondary endpoint, duration of response (DOR), would truncate the duration of response data to week 26.**

FDA clarified that the DOR data provided in the original BLA submission for study B3281006 should include DOR by treatment arm up to 52 weeks.

FDA also requested that the original BLA submission include the number of responding patients that were censored for DOR in each treatment arm.

Additional Product Quality Microbiology Comments

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 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 Module 1 of the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.
2. The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:

(b) (4)

[redacted]

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(b) (4)

Additional Clinical Pharmacology Comments

As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the BLA:

1. Include the rationale for the selected dose used in the PK study in the BLA (e.g., Module 2 Summary of Clinical Pharmacology document).
2. Include an evaluation of the impact of immunogenicity on the activity, safety, and pharmacokinetics, as is applicable, for the studies included in the application.
3. Submit all the PK bioanalytical method validation reports and bioanalytical study reports.
4. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range, as appropriate.
5. Include complete datasets for the PK studies. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.
6. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
7. Provide a tabulated summary (e.g., in Module 2) of the contact information for the clinical and analytical site(s) used in the study(ies) evaluating immunogenicity and in the PK similarity study(ies). Contact information for each facility should include: address, telephone and fax numbers; Clinical investigator's or responsible scientist's name and email.

Discussion: In regards to item 7, FDA accepted the Sponsor's proposal to include the requested information as part of the documents related to the Bioresearch Monitoring Program in Module 5 and the analytical site information in the Summary of Biopharmaceutics Studies and Associated Analytical Methods in Module 2.7.1.

Additional Immunogenicity Comment
To facilitate assessment of immunogenicity assays used in your clinical studies, the Agency advises Pfizer to submit standard operating procedures and validation reports of the immunogenicity assays to the IND prior the BLA submission. If multiple immunogenicity assays were used, please specify the assay(s) used in each clinical study.

Additional Discussion: The Sponsor acknowledged the information request send by FDA on February 22, 2018, requesting sample derived datasets including structure and variables for study B3281006. The Sponsor also noted the format of the datasets to be included for the studies (B3281001, B3281004, B3281006) in the BLA.

FDA acknowledged the Sponsor's response submitted February 27, 2018. DHP's review was ongoing with regard to dataset structure and content for study B3281006. The following comments are provided as a post-meeting addendum:

- **Please ensure that the define files and reviewer guide are clear, particularly as tabulation and analysis .xpt datasets for study B3281006 are not in standard cDISC format. For example, the treatment-emergent flag is unclear in the sample adverse event dataset.**
- **For each derived dataset, include a column for the ITT and safety populations.**

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Please refer to section 2.0 (DISCUSSION) of the meeting minutes.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion regarding the approach to developing the content for a REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions for Use) and, where applicable, the development of a Formal Communication Plan was held and it was concluded that a REMS was not necessary. However, the Sponsor should outline plans for their safety surveillance in the BLA submission.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients

(which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) 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/Guidaces/UCM360507.pdf). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the

content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

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

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

NONPROPRIETARY NAME

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

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

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

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

SUBMISSION FORMAT REQUIREMENTS

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues that require further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

Enclosure:
Sponsor's response to FDA's Meeting Preliminary Comments received via email on March 7, 2018.

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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/

YVETTE L KASAMON
04/06/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110426

MEETING MINUTES

Pfizer Inc.
Attention: Helen B. Hartman, Ph.D.
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Rd
Collegeville, PA 19426

Dear Dr. Hartman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-05280586 ("Rituximab-Pfizer").

We also refer to the meeting between representatives of your firm and the FDA on August 6, 2014. The purpose of the meeting was to obtain regulatory advice on the data generated to date and the proposed "Phase 3" development for PF-05280586, a proposed biosimilar product to US-licensed Rituxan.

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 contact, Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Angelo de Claro, M.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 3 Meeting

Meeting Date and Time: August 6, 2014, 2:00 PM – 3:30 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 110426
Product Name: PF-05280586 ("Rituximab-Pfizer")
Indication: Sponsor is seeking the same indications for which US-licensed Rituxan (rituximab) is approved.
Sponsor/Applicant Name: Pfizer Inc.

Meeting Chair: R. Angelo de Claro, M.D., Clinical Team Leader
Meeting Recorder: Kris Kolibab, Ph.D., Regulatory Project Manager

FDA ATTENDEES

Division of Hematology Products (DHP):
Ann T. Farrell, M.D., Director
R. Angelo de Claro, M.D., Clinical Team Leader
Nicole Verdun, M.D., Medical Reviewer
Kris Kolibab, Ph.D., Regulatory Project Manager
Theresa Carioti, MPH, Chief, Project Management

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP):
Nikolay Nikolov, M.D., Clinical Team Leader
Sarah Yim, M.D., Associate Director

Office of Clinical Pharmacology (OCP):
Nam Atiqur Rahman, Ph.D., Director

Office of Biostatistics (OB):
Chia-Wen Ko, Ph.D., Statistics Reviewer
Xiaoyu Dong, Ph.D., Statistics Reviewer
Ruthanna Davi, Ph.D., Statistics Reviewer

Office of Biotechnology Products (OBP):
Marjorie Shapiro, Ph.D., Chief
Mate Tolnay, Ph.D., Biologist

Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Team (TBBT):
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics
Sue Lim, M.D., Senior Staff Fellow
Neel Patel, Pharm.D., Regulatory Project Manager
Tyree Newman, B.S., Senior Regulatory Project Manager
Carla Lankford, M.D., Ph.D., Science Policy Analyst

SPONSOR ATTENDEES

Helen Hartman, Ph.D., Global Regulatory Lead
Beverly Ingram, Ph.D., Global Chemistry, Manufacturing Controls
Carol Kirchhoff, Ph.D., Biomanufacturing Sciences
Chee-Keng Ng, Ph.D., Analytical Research and Development
Xu Meng, Ph.D., Clinical Pharmacology
Bhardwaj Desai, M.D., Clinical
Bo Jin, Ph.D., Biostatistics
Dolca Thomas, M.D., Asset Lead
Michael Corbo, Ph.D., Biosimilars Chief Development Officer
Ira A Jacobs, M.D., Medical Affairs
Leah Isakov, Ph.D., Biostatistics
Barry Gumbiner, M.D., Clinical
Aili Cheng, Ph.D., Nonclinical Statistic
Andrew Rugaiganisa, MS, Statistics
Jason Williams, Senior Manager, Clinical Pharmacology

1.0 BACKGROUND

Pfizer Inc., requested a BPD Type 3 meeting with FDA on April 9, 2014 to obtain regulatory advice on the data generated to date and on the design of the proposed comparative clinical "Phase 3" study. On April 14, 2014, FDA sent Pfizer Inc. the meeting request granted letter.

After review of the briefing package, FDA sent preliminary responses to Pfizer's questions in an emailed letter dated August 4, 2014. In an email dated August 5, 2014, Pfizer provided clarifications and requested discussion of FDA responses to Clinical Questions 7A, 7B, 12, and Analytical Question 1. 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 **bold normal font**; and Pfizer's August 5, 2014, emailed responses also noted in *italics*. Summary of meeting discussions, if any, are found in 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 as the

Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

2. DISCUSSION

2.1. Quality

Question 1:

Based on the analytical similarity assessment conducted and data provided herein, Pfizer believes that the analytical similarity between rituximab-Pfizer and rituximab-US has been established to an extent that the potential biosimilar product can be assessed as highly similar to the reference product rituximab-US, with the analytical similarity data package, as being completed, sufficient to support (a) the initiation of the proposed phase 3 study (B3281006) from a safety perspective, and (b) the biosimilarity assessment of rituximab-Pfizer as part of the CMC requirements of a BLA under the 351(k) of the PHS Act. Does the Agency agree?

FDA Response to Question 1:

The analytical similarity data provided to date support the initiation of the proposed comparative clinical study ("Phase 3" study). A determination as to whether PF-05280586 is highly similar to US-licensed Rituxan will be made when the complete analytical package, including results from the new ADCC assay and validation studies demonstrating suitability of each assay, become available and are submitted for review either as part of a BPD Type 3 meeting or in your proposed 351(k) BLA.

However, we have concerns regarding the approach to analyzing the analytical similarity data to support a demonstration of highly similar. You proposed a graphical analysis to demonstrate analytical similarity between PF-05280586 and US-licensed Rituxan. For each of the two N-linked glycosylation attributes, test results of 11 representative PF-05280586 drug substance batches were plotted and compared against tolerance ranges. These tolerance ranges were derived from a bivariate tolerance region with 99% coverage and a 90% confidence level using 22 US-licensed Rituxan lots, and the numerical values were similar to the control limits of ±3SD. You conducted a similar approach for relative potency. The proposed approaches are essentially a visual inspection, not a formal statistical test. Even if all data from the biosimilar product were within the tolerance range of the US-licensed reference product, the mean values of each attribute could still fail an equivalence test. Thus, your proposed graphical analysis is insufficient to demonstrate analytical similarity between PF-05280586 and US-licensed Rituxan for quality attributes which are considered as Tier 1 and Tier 2 attributes as described below

With additional lots included, you conducted similarity assessments for N-linked glycosylation, charge heterogeneity, purity, aggregation, and relative potency between PF-05280586, US-licensed Rituxan and EU-approved MabThera presented as side-by-side comparisons of Mean, Range and %CV. Like the tolerance range approach, such

comparisons are not formal statistical tests. As a result, its decision rule on similarity is not statistically inference based.

To demonstrate analytical similarity between US-licensed Rituxan and EU-approved MabThera, you proposed significance testing on mean difference. Such a test is applicable when the aim is to detect differences, not to demonstrate similarity. In addition, significance testing is easier to have favorable results for small sample sizes or large variability. For these reasons, significance testing is inappropriate for demonstrating similarity.

We currently recommend that you use a statistical approach to evaluate quality attributes of proposed biosimilar products that is consistent with the risk assessment principles set forth in the International Conference on Harmonisation Quality Guidelines Q8, Q9, Q10, and Q11. Consistent with these principles, your program should implement an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used.

One approach to determining the tier to which a particular quality attribute would be assigned would depend upon a criticality risk ranking of quality attributes with regard to their potential impact on activity, PK and/or PD, safety, and immunogenicity with quality attributes being assigned to tiers commensurate with their risk.

For your program, equivalency testing would be recommended for quality attributes with the highest risk ranking (Tier 1) and generally would include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. We recommend that you consider the use of quality ranges (mean +/- X σ, where X should be appropriately justified) for assessing quality attributes with lower risk ranking (Tier 2), and an approach that uses raw data/graphical comparisons for quality attributes with the lowest risk ranking (Tier 3).

In addition to criticality, other factors should be considered in assigning quality attributes and assays to a particular tier using this approach. This approach includes, but it is not limited to, the levels of the attribute in both the reference product and proposed biosimilar product (as determined by your testing), the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute.

FDA also recommends that you carefully assess your analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that PF-05280586 is highly similar to the reference product. This could include, for example, considering the ages of the PF-05280586 and reference product lots tested, optimizing assays and pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate.

We think it would be appropriate for you to consider a statistical approach, such as the one set forth below based on FDA's current thinking on the topic, to evaluate certain quality attributes of the proposed biosimilar and the reference product. You may propose alternative statistical approach(es) to evaluate quality attributes and support a demonstration that PF-05280586 is highly similar to US-licensed Rituxan.

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

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

1. **Tier 1 (Equivalence Test): One needs to test against the following null hypothesis.** $H_0 : \mu_B - \mu_R \leq -\delta$ **or** $\mu_B - \mu_R \geq \delta$ **where** μ_B **and** μ_R **are the mean responses of the proposed biosimilar and reference product lots, respectively, and δ > 0 is the equivalence margin. The test should be based on the normal distribution, unless the data clearly deviate from the normal distribution.**

   Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if the (1-2α)100% two-sided confidence interval of the mean difference is within (– δ, δ). In this context, the equivalence margin, δ, would be a function of the variability of the reference product as identified in studies by the biosimilar applicant (σ_R**).**

2. **Tier 2 (Quality Range Approach): The quality range of the reference product for a specific quality attribute is defined as (**$\hat{\mu}_R - X\hat{\sigma}_R$ **,** $\hat{\mu}_R + X\hat{\sigma}_R$**), where the standard deviation multiplier (X) should be appropriately justified.**

   Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if a sufficient percentage of test lot values (e.g. 90 percent) fall within the quality range.

3. **Please note that each lot contributes one value for each attribute being assessed. Thus,** σ_R **refers to the standard deviation of those lot values of the reference product.**

4. **Ideally, the reference variability,** σ_R**, should be estimated from testing different lots than those used in statistical equivalence test. This may be a challenge when there are a limited number of lots. You should provide a plan for how the reference variability,** σ_R**, will be estimated supported by a justification for the approach, and identify the lots that will be used.**

5. **We would also recommend that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot, and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.**

6. **Please note that high assay variability would not be a justification for a large σ_R. In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.**

7. **In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range.**

One potential statistical approach to evaluate quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g., c * σ_R). The constant c would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, we selected $\delta = 1.5\ \sigma_R$ for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90% confidence interval about the difference in sample means lies within (-1.5 σ_R, 1.5 σ_R). If 10 biosimilar and 10 reference product lots are available, this test would have approximately 84% power when the true underlying mean difference between the proposed biosimilar and reference product lots was equal to σ_R /8, assuming a test with $\alpha = 0.05$.

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

We note that you are proposing to use EU-approved MabThera as the sole comparator in your comparative clinical study (Study B3281006). We remind you that to justify the relevance of this data to a demonstration of biosimilarity to US-licensed Rituxan, you will need to establish an adequate scientific bridge (see also our response to Question 8). The type of bridging data needed to provide adequate scientific justification for this approach would likely include a bridging clinical PK and/or pharmacodynamics (PD) study, as well as direct physicochemical comparison of all 3 products: US-licensed Rituxan to PF-05280586, EU-approved MabThera to PF-05280586, and US-licensed Rituxan to EU-approved MabThera. All three comparisons should meet the pre-

specified acceptance criteria for analytical and PK similarity. The adequacy of this scientific justification and bridge to the US-licensed reference product will be a review issue. Therefore, we recommend that the three-tier approach described above to demonstrate analytical similarity should be applied to the comparison between PF-05280586 to US-licensed Rituxan, PF-05280586 to EU-approved MabThera, and between US-licensed Rituxan and EU-approved MabThera.

Discussion:

Pfizer provided a Word document with clarification points (A-G) to facilitate discussion at the meeting.

Clarification A:

Pfizer confirmed the items outlined in FDA's response to Question 1 would be addressed, and that data from the analysis of additional lots of US-licensed Rituxan, EU-approved MabThera and PF-05280586 would be submitted in the BLA. Pfizer asked if their proposed analytical similarity package would align with FDA's expectations for the analytical similarity data to be submitted in a 351(k) BLA.

FDA agreed that Pfizer's plan in terms of the proposed content and data presentation seemed reasonable; however, the adequacy of the data to support a demonstration that PF-05280586 is highly similar to US-licensed Rituxan would be a review issue.

Clarification B:

Pfizer asked for confirmation that characterization assays used in the analytical similarity exercise should be suitable to detect differences, and do not have to be validated as per ICH Q2(R1). FDA stated that their statement that "validation studies demonstrating suitability of each assay" was not intended to refer to validation of analytical procedures as per ICH Q2(R1). FDA indicated that an understanding of method feasibility and variability, especially for potency-related functional assays or methods where the effect of biological elements contributed to variability, should be included in the BLA.

Clarification C:

Pfizer requested guidance on how to implement the recommendation to randomly split the reference product data for setting the margins and for testing for equivalence. FDA recommended that Pfizer submit a proposal to FDA for review and comment. The Agency further recommended that Pfizer submit to the IND the quality attribute (QA) risk ranking, assay methodologies, justification for tier assignment, outline of the challenges, and statistical methods to be applied prior to conducting the full statistical analysis. Pfizer noted that they are considering approaches to ranking quality attributes and conducting statistical testing in all of their biosimilar development programs. The Agency noted that Pfizer should consider their plans to extrapolate clinical data from one condition of use to other conditions of use when considering the ranking of attributes, and stated that the considerations for

Pfizer's proposed biosimilars to reference products such as Rituxan and Remicade may be different from other products, since the conditions of use for which Pfizer was proposing to seek to extrapolate from for these products are more diverse compared to other programs where only one therapeutic area is considered.

Clarification D:

Pfizer asked for clarification regarding justification for "X", and how to determine the appropriateness of the final quality ranges as determined by the suggested methods.

The Agency indicated that Pfizer should consider a number of relevant factors when defining the value of "X", not just statistical considerations, such as the age of the reference product, the potential for a QA to change over the shelf-life, different impacts on MOA, and the method variability. The value of 'X" and the corresponding justification would differ among QAs assigned to statistical tier 2.

Clarification E:

Pfizer asked for clarification as to whether an equivalence test conducted based on 90% confidence interval and appropriate equivalence margins at the 5% significant level and that ensures adequate power (e.g. ≥ 80 %) would preclude further justification by the final manufacturing control strategy.

In order to account for potential multiplicity effect when more than one quality attribute whose data are amenable to statistical treatment are categorized as Tier 1, Pfizer asked if similar adjustments could be made to the confidence level in order to achieve sufficient overall power. The Agency stated that a multiplicity adjustment is not expected. For each quality attribute in Tier 1, the equivalence test should be based on a 90% confidence interval of the mean difference.

Clarification F:

Pfizer asked for confirmation from FDA that data that does not satisfy required statistical assumptions, such as independent and identically distributed data, should be assigned to the Tier 3.

The Agency advised that Pfizer should justify why an attribute and/or an assay methodology precludes certain statistical approaches, even if the attribute has a high risk ranking. However, the Agency emphasized the tiers are an approach to statistical testing, and that Tier 3 is not a "catch-all" when data are not amenable to statistical analysis. Quality attributes should be ranked, but then, the appropriate statistical approach (tier) should be considered based on attribute and/or assay considerations. The Agency agreed that not all quantitative data would need to be subject to statistical testing.

Clarification G:

Given that some quality attributes are inter-related, for example charge variants (e.g. acidic species, main, and basic), Pfizer inquired if the Agency could recommend a statistical approach for the analysis of these inter-related quality attributes.

The Agency stated that Pfizer should propose an approach and justify why it would be acceptable in the specific setting of inter-related quality attributes. Further internal discussion would be needed once a specific issue was identified.

Question 2:

The sponsor believes that the presentations (100 mg/10 mL and 500 mg/50 mL) of rituximab-Pfizer are fully representative of one another, and as such data generated with one is equally relevant to the other. Therefore data from clinical studies completed with the rituximab-Pfizer 500 mg/50 mL presentation is considered adequate to support the registration of both the 500 mg/50 mL and 100 mg/10 mL presentations. Does the Agency agree?

FDA Response to Question 2:

We agree that the 100 mg/10 mL and 500 mg/50 mL presentations are fully representative of one another and that clinical data generated with one are equally relevant to the other to support the approval of both presentations. However, CMC data for both presentations need to be submitted with the BLA.

Discussion:

No discussion occurred.

Question 3:

The rituximab licensed product label includes instruction to dose based on body surface area (BSA, oncology indications) without a maximum dose specified. For the purposes of release and stability acceptance criteria, a maximum clinical dose must be identified; as such Pfizer believes that it is appropriate to propose a maximum clinical dose based on a likely maximum BSA. Does the Agency agree?

FDA Response to Question 3:

We agree that setting of release and stability acceptance criteria can be based on an appropriate maximum BSA and corresponding maximum dose.

Discussion:

No discussion occurred.

Question 4:

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 proposed biosimilar is distinct from that of the innovator product, there should be no expectation to match the innovator product in process-related impurities. Instead, 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. Additionally, host cell protein impurities will be assessed by non-immunologic, orthogonal approaches to determine to what extent the proposed biosimilar and innovator products may differ and whether the difference presents additional risk to patient safety that could impact biosimilarity. Does the Agency agree with the rationale and approach outlined in the briefing document?

FDA Response to Question 4:

Please refer to the June 21, 2014 meeting minutes and discussion for your IND 110427 BPD 2 meeting, held on April 8, 2014, regarding Pfizer's approach to process-related impurities. As captured in the meeting minutes, FDA advised that "we consider the advice provided herein in the context of IND 110427 regarding your approach to assessing process-related impurities in the context of biosimilar development to be applicable to your other biosimilar development programs to which you referred (INDs 110426, (b) (4)). " Subject to this prior advice, we agree with the rationale and approach outlined in the briefing document regarding process-related impurities.

Discussion:

No discussion occurred.

2.2. Nonclinical

Question 5:

Does the Agency agree that the in vivo nonclinical program for rituximab-Pfizer is sufficient to support both Phase 3 development for rituximab-Pfizer, and the registration requirements for rituximab-Pfizer as a biosimilar under 351(k) of the PHS Act?

FDA Response to Question 5:

The nonclinical program for PF-05280586 is acceptable to support initiating the comparative clinical study, and for BLA filing. However, a final determination as to whether the totality of the data, including the nonclinical data, is sufficient to support a demonstration of biosimilarity will be made during the review of your proposed 351(k) BLA.

Discussion:

No discussion occurred.

2.3. Clinical

Question 6:

Pfizer believes that the PK results from Study B3281001 have established the PK similarity of rituximab-Pfizer to rituximab-US and to rituximab-EU; and of rituximab-EU to rituximab-US, therefore will fulfill the rituximab-Pfizer PK characterization and similarity requirement for a BLA under the 351(k) of the PHS Act. Does the Agency agree?

FDA Response to Question 6:

We agree. It appears that the PK similarity of PF-05280586 to US-licensed Rituxan, PF-05280586 to EU-approved MabThera, and US-licensed Rituxan to EU-approved MabThera have been demonstrated. However, a final determination regarding the demonstration of PK similarity will be a review issue once your 351(k) application is submitted.

Discussion:

No discussion occurred.

Question 7:

A) Does the Agency agree that the clinical data from Study B3281001 support the initiation of the proposed Phase 3 Study B3281006 with rituximab-Pfizer from a safety perspective?

B) Does the Agency agree that the clinical data from Study B3281001 have demonstrated no clinically meaningful differences in PK, safety and immunogenicity between rituximab-Pfizer and rituximab-US and therefore support initiation of the proposed Phase 3 Study B3281006 from a similarity perspective?

FDA Response to Question 7A:

The clinical data from Study B3281001 appear reasonable from a safety perspective to support the initiation of the proposed comparative clinical study, B3281006. However, we note that the ACR20/50/70 response rates of the PF-05280586 treatment arm are numerically lower as compared with the responses in the US-licensed Rituxan and EU-approved MabThera arms. Further, the differences in ACR response rates appear to be more evident than the DAS28-CRP results. We acknowledge that Study B3281001 was not primarily designed to compare efficacy, however the noticeable trends toward worse clinical response with PF-05280586 compared with the US-licensed Rituxan and EU-approved MabThera arms raise questions about potential differential efficacy in the RA population, which could be relevant in the review of the totality of the evidence

to support a demonstration of biosimilarity and also for extrapolation to other conditions of use, including additional rheumatologic indications.

We recommend that you explore the potential causes of the observed differences in clinical response. It is also important to explain why the numerical differences appear more evident with the ACR response rates than with the continuous DAS28-CRP. Examples of analyses you may consider to address these concerns include but are not limited to: cumulative distribution analysis of ACR response at different time points, as measured by ACRn, where ACRn is a continuous variable; analysis of the core ACR and DAS28 components. For all analyses, provide estimated differences between treatment arms, in addition to confidence intervals around those differences.

If analytical and PK similarity between US-licensed Rituxan and EU-approved MabThera is demonstrated, you may then estimate differences in response between the PF-05280586 group and a pooled comparator group consisting of both patients treated with US-licensed Rituxan and with EU-approved MabThera. This would lead to a larger comparator group and therefore greater sensitivity to identify differences, if they exist.

FDA Response to Question 7B:

While we agree that PK similarity appears to have been demonstrated, a demonstration of PK similarity alone does not provide demonstration of no clinically meaningful differences in the context of this development program. In addition, there is residual uncertainty regarding the demonstration of no clinically meaningful differences in Study B3281001 because of the differences seen in the ACR20/50/70 responses between PF-05280586 compared to US-licensed Rituxan and EU-approved MabThera arms. Refer to FDA's response to Question 7A.

A determination of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan will be made based on the totality of the evidence, including data from the planned Study B3281006.

Discussion:

Clarifications A and B:
Pfizer explained that a possible cause of the numerical difference in ACR response was due to an imbalance in baseline characteristics between US-licensed Rituxan, EU-approved MabThera and PF-05280586 study arms, with more severe disease activity in the US-licensed Rituxan compared to the PF-05280586 arm at baseline. Pfizer also showed analyses to support their claim that differences in the gating of joint counts and HAQ could also explain the apparent differences between ACR20 and DAS28. Pfizer also stated that the new population PK/PD analysis suggests that point estimates of mean simulated differences were within the boundary of either DAS28 or ACR20/50/70 PD/clinical endpoints.

The Agency acknowledged the limitations of study B328100, namely that it was not designed to assess efficacy, and stated the results of study B3281001 would be reviewed as part of the totality of the data. Regarding the population PK/PD analysis, FDA commented that the endpoints of area under the effect curve of DAS28 or ACR20/50/70 used are not the protocol specified endpoints. To mitigate the effect of imbalances at baseline on the response, FDA recommended the Pfizer perform a propensity score analysis on the DAS28 and ACR20/50/70 clinical endpoints. To evaluate the impact of differences in gating, FDA recommended a cumulative responder analysis and stated that a reference for this type of analysis could be provided as a post-meeting note. The FDA also recommended the use of confidence intervals in addition to point estimates to describe the treatment effect.

Post-meeting Note:
The following reference is provided regarding the cumulative responder plot:

J.T. Farrar, R. H. Dworkin, M. B. Max, Use of the Cumulative Proportion of Responders Analysis Graph to Present Pain Data Over a Range of Cut-Off Points: Making Clinical Trial Data More Understandable. *Journal of Pain and Symptom Management*, 31 (4) (2006), pp.369-377).

Question 8:

A) *Does the Agency agree that the analytical similarity data comparing rituximab-US and rituximab-EU have established an acceptable analytical bridge to support the use of rituximab-EU as the sole comparator in the proposed Phase 3 trial from a similarity perspective?*

B) *Does the Agency agree that the PK similarity data comparing rituximab-US and rituximab-EU from study B3281001 have established an acceptable PK bridge and supports the use of rituximab-EU as the sole comparator in the proposed Phase 3 trial from a similarity perspective?*

FDA Response to Question 8:

We agree that based on the analytical and PK similarity data provided to date, it appears reasonable to use EU-approved MabThera as the sole comparator in Study B3281006. However, a final assessment regarding adequacy of the scientific bridge, supported by the analytical and PK similarity data, will be a review issue once all the data become available and are submitted for review either as part of a BPD Type 3 meeting or in your proposed 351(k) BLA. Refer to also to our response to Question 1 for additional information on establishing analytical similarity.

Discussion:

FDA agreed with Pfizer's statement that the discussion within Question 1 regarding the demonstration of analytical similarity of PF-05280586 to the reference product was also applicable to the demonstration of the scientific bridge between US-licensed Rituxan and EU-approved MabThera.

Question 9:

Does the clinical trial design for the Phase 3 Study B3281006 support the requirements for demonstrating no clinically meaningful differences in efficacy and safety for the potential biosimilar rituximab-Pfizer compared to rituximab-EU under Section 351(k) of the PHS Act?

A) Does the FDA agree with the primary endpoint: ORR at Week-26 of rituximab-Pfizer and rituximab-EU based on central radiology review in accordance with the revised response criteria for malignant lymphoma?

B) Does the FDA agree with the study population (FL LTB), including the use of the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria with modification (i.e., slightly abnormal serum LDH and β2-microglobulin levels, based on the baseline patient characteristics of the Ardeshna study?

C) Does the FDA agree with the use of a dosing regimen of 375 mg/m^2 weekly x 4 weeks?

D) Given the extensive PK data from the B3281001 study, does the FDA agree that the PK analyses proposed for Study B3281006 will be adequate?

E) Does the FDA agree that the immunogenicity assessment proposed for B3281006 is adequate for the biosimilarity exercise?

F) Does the FDA agree that duration of 1 year for assessment of comparative immunogenicity is adequate for the oncology indications as well as the inflammation indications given the immunogenicity data accrued in RA Studies B3281001 and B3281004?

FDA Response to Question 9:

The adequacy of the proposed comparative clinical study to support a demonstration of no clinically meaningful differences will be a review issue. Submit your final study protocol to the IND for review prior to starting the proposed comparative clinical study, Study B3281006.

Based upon the draft study protocol included in the meeting package:

9A. The proposed primary endpoint is acceptable.

9B. While we agree with the proposed study population, you should provide further justification for use of the modified GELF criteria, taking into account other clinical trials in the low tumor burden follicular lymphoma population in addition to the one randomized trial you have referenced (Ardeshna).

9C. The dosing regimen proposed is acceptable.

9D. The proposed PK plan is acceptable.

9E. The proposed immunogenicity sampling schedule is acceptable. We agree with your tiered approach of screening, confirmation, and endpoint titer determination. We note that you developed two assays, one to detect Abs against PF-05280586 and one to detect Abs against US-licensed Rituxan and EU-approved MabThera, and that samples confirmed to be positive in one assay are tested in the other assay. Although this approach appears acceptable, we have not completed our review of the assay validation data and cannot comment on assay performance at this time.

9F. The proposed duration of assessment is acceptable.

Discussion A-F:

No discussion occurred.

Question 10:

Does the Agency agree that if the comparative safety and efficacy data in an LTB first-line monotherapy setting demonstrates similarity between the tested products, the data would fully support the requirements for the evaluation of similarity in efficacy, safety and immunogenicity under Section 351(k) of the PHS Act?

FDA Response to Question 10:

The overall study design in a low follicular lymphoma population appears acceptable.

The data from Study B3281006, in combination with the data from your other clinical studies, may be sufficient to support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan. However, the adequacy of the data will be a review issue. You will also 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. Refer also to our response to Question 13.

Discussion:

No discussion occurred.

Question 11:

Does the Agency agree with the proposed margin (-16%, 16%) in ORR difference for the similarity assessment in the planned Phase 3 Study B3281006?

FDA Response to Question 11:

Yes, we agree that the proposed margin is acceptable.

Discussion:

No discussion occurred.

Question 12:

Pfizer does not believe a pediatric program is warranted. Does the Agency agree?

FDA Response to Question 12:

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21U.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/Guidaces/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.

You must address PREA for every indication for which you seek licensure, and we strongly encourage you to submit a comprehensive iPSP 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. Requested deferrals or waivers in the iPSP will not be formally granted or denied until the product is licensed.

Discussion:

To address the PREA requirements, the Agency stated that the iPSP submission must be complete and address PREA for all the indications for which Pfizer intends to seek licensure. FDA noted that granulomatosis with polyangiitis and microscopic polyangiitis were not included in the submission, and that PREA would need to be addressed for these conditions if Pfizer intends to seek licensure for these indications. The Sponsor acknowledged FDA's comments and stated their plan to submit the iPSP within 60 days of the meeting.

2.4. Cross-functional, Regulatory, and/or other

Question 13:

Does the Agency agree that the proposed data package in totality containing CMC and nonclinical comparability data, Phase 1 PK/PD study in RA patients, and the proposed Phase 3 study evaluating efficacy and safety in LTB FL is sufficient to provide extrapolation to all indications approved for the licensed product, with respect to a) nonclinical data, and b) clinical data?

FDA Response to Question 13:

If PF-05280586 meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the biosimilar product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, you would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- **the mechanism(s) of action in each condition of use for which licensure is sought; this may include:**
  - **the target/receptor(s) for each relevant activity/function of the product;**
  - **the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;**
  - **the relationships between product structure and target/receptor interactions;**
  - **the location and expression of the target/receptor(s);**

- **the PK and bio-distribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);**
- **differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities); and**
- **any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.**

We encourage you to address the factors above as part of your plan to extrapolate from the studied condition of use to other conditions of use for which the reference product is licensed.

The overall development plan appears acceptable. The adequacy of the entire data and information package to support extrapolation to all indications for which US-licensed Rituxan is licensed and for which you seek licensure will be a review issue at the time of submission of your proposed 351(k) BLA application.

Discussion:

No discussion occurred.

Question 14:

As previously noted, Pfizer is proposing to conduct the pivotal efficacy and safety trial in an off-label indication. We recognize that per the "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" guideline the proposed biosimilar can only be approved for conditions of use that "have been previously approved for the reference product". The guidelines, however, are unclear as to the extent that biosimilar clinical program will be reflected in the biosimilar label. Regarding the rituximab-Pfizer label, will the label include the clinical safety, efficacy, and immunogenicity data which will be accrued in the LTB FL population?

FDA Response to Question 14:

We cannot provide a response to your question at this time, but will provide a response in an appropriately timely manner considering the stage of the development program for PF-05280586.

Discussion:

No discussion occurred.

3.0 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor provided the attached Word document and slide deck for the meeting.

39 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this 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/

ROMEO A DE CLARO
09/05/2014