CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761118Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114729

MEETING MINUTES

Pfizer Inc.
500 Arcola Rd.
Collegeville, PA 19426

Attention: Chengyu Gao
Senior Manager, Global Regulatory Affairs

Dear Mr. Gao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06410293.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2018. The purpose of the meeting was to discuss the content and format of the submission of 351(k) BLA for PF-06410293.

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) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4227388

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	BPD Type 4
Meeting Date and Time:	June 12, 2018 at 12:00 PM
Meeting Location:	FDA White Oak, Bldg 22, Rm 1419
Application Number:	IND 114729
Product Name:	PF-06410293
Indication:	PF-06410293 is being developed for the same indications as approved for US-licensed Humira
Sponsor Name:	Pfizer, Inc.
Meeting Chair:	Nikolay P. Nikolov, MD
Meeting Recorder:	Jessica Lee, PharmD

FDA ATTENDEES

Nikolay P. Nikolov, MD, Associate Director for Rheumatology, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Rachel Glaser, MD, Clinical Team Leader, DPARP
Chana Fuchs, PhD, Team Leader, Division of Biotechnology Review and Research IV
Jee Chung, PhD, Biologist, Division of Biotechnology Review and Research IV
Anshu Marathe, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II
Mohammad (Abir) Absar, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II
Andrew Goodwin, PhD, Pharmacology/Toxicology Supervisor, DPARP
Dong Zhao, PhD, Pharmacology/Toxicology Reviewer, DPARP
Greg Levin, PhD, Lead Mathematical Statistician, Division of Biometrics II
Ginto Pottackal, PhD, Mathematical Statistician, Division of Biometrics II
Tianhua Wang, PhD, Mathematical Statistician, Division of Biometrics VI
Tianjiao Dai, PhD, Mathematical Statistician, Division of Biometrics VI
Stacey Ricci, PhD, Toxicologist, Therapeutic Biologics and Biosimilars Staff
Sue Lim, MD, Team Leader, Therapeutic Biologics and Biosimilars Staff
Saharat Patanavanich, PharmD, Safety Regulatory Project Manager, OSE
Teresa McMillan, PharmD, Safety Evaluator, DMEPA, OSE
Sarah Vee, PharmD, Team Leader, DMEPA, OSE

Reference ID: 4220388

Kathleen Fitzgerald, Nurse Consultant, Lead Reviewer, CDRH
Patricia Hughes, PhD, Supervisory Microbiologist, Microbiology Assessment Branch IV
Maxwell Van Tassell, PhD, Microbiologist, Microbiology Assessment Branch IV
Joel Welch, PhD, Review Chief, Division of Biotechnology Review and Research IV
Kevin Clark, MD, Medical Officer, Division of Dermatology and Dental Products
Jessica Lee, PharmD, Senior Regulatory Project Manager, DPARP

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Independent Contractor, Eastern Research Group, Inc.

SPONSOR ATTENDEES
Chengyu (Cash) Gao, Global Regulatory Affairs, US
Huihan (Christy) Meng, Global Regulatory Affairs, US
Lee Pitts, Global Regulatory Affairs, CMC
Paul Brown, Co-Development Team Lead
Matthew Thompson, PhD, Analytical Research and Development
James McColgan, Pfizer Global Supply, Andover, Director Site Technical Services
Ling Lu, Sr. Principal Scientist, Design Control Lead, Formulation and Process Development
Kirsten Paulson, Global Regulatory Affairs, CMC- Medical Devices
Tracy Dianis, Global Regulatory Affairs, Director, Biosimilars

SPONSOR ATTENDESS by Phone
Vincent Amoruccio, Pfizer Global Biometrics and Data Management
Aili Cheng, PhD, CMC Statistics, Pfizer Worldwide Research and Development
Carol Cronenberger, PhD, Clinical Pharmacology Lead
K. Lea Sewell, MD, Global Clinical Lead
Anthony (Tony) L. Young, Pfizer Pharmaceutical Research and Development
Wuyan Zhang, PhD, Biostatistics

1.0 BACKGROUND

In a submission dated April 13, 2018, Pfizer requested a Biosimilar Biological Product Development Type 4 Meeting to discuss the content and format of a 351(k) BLA submission for PF-06410293. The meeting was granted on April 25, 2018. Pfizer's questions from the briefing document dated April 13, 2018 are listed below in *italics*, FDA responses and meeting Discussions are provided in normal font.

FDA sent Preliminary Comments to Pfizer on June 8, 2018.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Pfizer 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 PF-06410293 351(k) BLA as presented in Appendix 2 of the Meeting Package Material such that it meets the Agency's expectations for e-CTD submission?

FDA Response to Question 1:

We note your proposal to include the agreed initial pediatric study plan (iPSP) in the original BLA submission in Section 1.9.1. We further note that your iPSP was submitted on April 6, 2018. Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. As discussed in *Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf, a sponsor should not submit a marketing application until agreement has been reached on the iPSP. The Agency cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. It should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP.

Section 3.2.R.1 *Executed Production Records* should include Batch records for the PFP assembly process.

The proposed information to be submitted appears otherwise reasonable.

Discussion to Question 1:

The Sponsor proposes to provide one representative executed batch record for the 40 mg/0.8 mL PFP configuration of PF-06410293 DP in Section 3.2.R.1 Executed Production Records and the Agency found the proposal acceptable. The FDA reminded Sponsor that the timing of the submission must account for the iPSP process.

Question 2:

Does the 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 3 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 to Question 2:

The "351(k) roadmap" navigation tool to the data within the BLA appears reasonable. The roadmap navigation tool does not identify that ADCC activity using FcγRIIIa 158 F/F donor cells will be included in the Biological Activity: Fc Domain section in modules

Reference ID: 4227388

2.3.R.3 and 3.2.R.3. We understand that you will present an update on the development of these data; however, this information should be included in these sections.

Discussion to Question 2:

The Sponsor stated that the ADCC studies using FcgRIIIa 158 F/F (refer to slide 6 of attachment) are complete and the results will be submitted in the BLA. In addition, the ADCC assay using FcgRIIIa 158F/F study and supporting method qualification studies will be included in the 351(k) roadmap. The Agency found the proposal acceptable.

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:

Regarding the eCTD sections for immunogenicity: You proposed to submit summary of safety and immunogenicity data and validation reports for immunogenicity assays in section 2.7.4 *Summary of Clinical Safety* and section 5.3.1.4 *Reports of Bioanalytical and Analytical Methods for Human Studies*, respectively. For your BLA, the integrated immunogenicity summary in section 2.7.4 that is derived from more than one study should include:

a) An immunogenicity risk assessment specific to your product.

b) Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods you developed in your program.

c) Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your comparative clinical study.

d) Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed.

e) Summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/treatment efficacy/safety (adverse-events) data.

f) Traceability of drug product lots used in all your clinical studies.

g) If different assays were used during clinical development, identify which assays were used for which studies or patient groups.

See also the additional Product Quality Microbiology comments

Discussion to Question 3:

The Sponsor provided a table of the location of immunogenicity information that will be in the BLA submission on slide 5 in the attached document of Section 6.0. The Agency discussed with the Sponsor that the proposed locations of the data and summaries are reasonable, but also requested that the Sponsor provide a reviewer guide with links in the BLA submission.

Question 4:

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

FDA Response to Question 4:

We agree.

Discussion to Question 4:

None.

Question 5:

Does FDA have any feedback with the proposed labeling concept for PF-06410293 to support the BLA submission?

FDA Response to Question 5:

It is premature to provide comments on the proposed labeling concept at this time. Submit your draft proposed labeling for PF-06410293 in PLR format with your BLA application. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on the draft proposed labeling during review of your BLA.

Discussion to Question 5:

None.

Question 6:

Does FDA have any feedback on the proposed organization of CTD Section 3.2.R.3 including cross references to other sections in Module 3, as shown in Appendix 4?

FDA Response to Question 6:

Reference ID: 4220388

The proposed organization of CTD section 3.2.R.3 as shown in Appendix 4 of the meeting package appears acceptable. However, we have the following comments regarding the descriptions provided in the "Summary of Planned Content and Format" column of the table outlining the structure of section 3.2.R.3:

a) Section 3.2.R.3.1.2 states that information regarding all the lots enrolled in the analytical study will be provided including lot selection criteria. For each PF-06410293 drug substance (DS) lot and drug product (DP) lot, provide information on the use of the lot, corresponding DS or DP lot number, manufacturing site, scale and/or process, date of manufacture, and presentation of the drug product (PFS, PFP, or vial). For DP lots, include information on the source of DS used to manufacture the DP lot. For US-licensed Humira and EU-approved Humira lots, information should also include expiration date of the lot and identification of lots used in the specific clinical or analytical components of the similarity assessment.

b) Section 3.2.R.3.1.3 states that description of the analytical methods used for similarity assessment will be provided in tabular format, whereas description and validation of analytical methods common to similarity assessment and PF-06410293 drug substance release are provided in section 3.2.S.4.1 and 3.2.S.4.3. For ease of the BLA review, a table listing all methods used for analytical similarity that includes methods also being used for DS and DP release testing should be provided, with some distinctive marking (e.g. asterisk) for those assays used for DS and DP release testing. The table should also include active hyperlinks to the assay's respective validation reports, qualification reports, method transfers (where applicable), and full method protocols.

c) Section 3.2.R.3.5 Appendix states that data will be provided in tabular format. In addition to the data in tabular format, include calculations, for example; mean and standard deviation of the tabular data where applicable, and raw data, e.g. chromatograms, electropherograms, gels, concentration-response curves, etc., for all the methods used in the similarity assessment. Include figures containing graphical presentation of each quality attribute to enable a visual comparison of the individual results across the three groups (PF-06410293, US-licensed Humira, and EU-approved Humira).

Discussion to Question 6a:

The Sponsor proposed locating information about lots used in the similarity assessment for PF-0610293 in 3.2.R.3.1.2 and the reference product in 3.2.R.3.5. The Agency agreed that these locations are acceptable.

Discussion to Question 6b:

The Sponsor proposed classifying methods used for the similarity assessment into three groups as indicated in slide 8 and 9 of the attachment. Generally, the Agency found the proposal acceptable, but requested that for qualitative assays the method summaries include sufficient

Reference ID: 4227388

information and data to enable evaluation of the adequacy of the method performance to support their intended use.

Discussion to Question 6c:

In discussion of the presentation and location of data in the BLA as outlined on slide 10, the Agency asked the Sponsor to also provide justification for why lots were selected for analysis in cases where individual lots or a subset of lots were tested.

Question 7a:

Do the files listed in Table 4 meet the Agency's expectation for clearly communicating details of the analytical similarity statistical analysis presented in 3.2.R.3?

FDA Response to Question 7a:

Yes, as long as the files and R code can be recognized and located according to the information provided in Table 4 and the results of analysis can be re-produced by running the R code provided by the sponsor.

Discussion to Question 7a:

None.

Question 7b:

Does the Agency accept the file names and file extensions as shown in Table 4?

FDA Response to Question 7b:

Yes, we do.

Discussion to Question 7b:

None.

Question 7c:

Does the Agency agree with the proposed location of these files in Section 3.2.R.3.5?

FDA Response to Question 7c:

Yes, we agree.

Discussion to Question 7c:

None.

Question 8:

Does the FDA agree [redacted] *? If not, are there alternative strategies that can be employed to minimize duplicative efforts related to the potentially overlapping PAIs?*

FDA Response to Question 8:

Although in principle it may be possible [redacted] the adequacy of this proposal would depend on the exact time of submission of the PF-06410293 BLA during Q3 2018, as we would require sufficient time to review [redacted] the DS manufacturing sections prior to an inspection. FDA does not agree [redacted]

Discussion to Question 8:

The Sponsor requested the Agency [redacted] The Agency and the Sponsor discussed [redacted] The Agency could not commit [redacted] in support of PF-0610293.

Question 9:

Pfizer is seeking a mechanism to facilitate FDA review [redacted] *Does FDA have feedback on this proposal?*

FDA Response to Question 9:

In principle, it may be possible to perform a review [redacted] A final decision on the need to review specific data will be made during BLA review, and will depend on the testing site information, methods executed at a particular site, and [redacted] BLA submission.

Discussion to Question 9:

None.

Question 10:

Does the FDA have any feedback on the proposed structure and format of the PF-06410293 prefilled syringe and prefilled pen device leaflets as presented in Appendix 5 of this meeting package such that it meets the Agency's expectations for e-CTD submission?

FDA Response to Question 10:

We acknowledge that you have proposed to place your Human Factor (HF) submissions in Module 3. However, to help better facilitate the review of your submission, we recommend all HF development including simulated-use studies be placed in Section 5.3.5.4.
As previously communicated (Meeting Minutes dated April 5, 2018), a safety assessment of leachables (and extractables as appropriate) from the container closure system should be available in the BLA. Clarify where in the submission the E&L study reports and safety assessments will be.

Discussion to Question 10:

The Agency recommended that the Sponsor provide the Human Factors information in section 5.3.5.4 of the BLA submission to facilitate review and ease of location. The Sponsor agreed to the Agency request.

The Sponsor noted that they intend to submit a summary of the E&L study and safety assessment in Module 3.2.P.2.4 and that the corresponding reports would be available upon request. The Sponsor noted that the study reports may not be finalized by the time of the planned BLA submission. The Agency recommended that the E&L study reports and safety assessment reports also be included in the BLA submission.

CDRH Comments:

Your proposed outline of the combination product application information format for the prefilled syringe and prefilled pen device is aligned with our expectations for the eCTD submission. Provide a complete and detailed description of the device constituent design inputs and outputs per 21 CFR 820.30, specifically the design requirements/specifications documentation with objective acceptance criteria in your application. Ensure that you clearly describe the acceptability of your design inputs and outputs within the context of the intended use of your combination product. The design inputs and outputs should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, environment of use, etc. In addition to the proposed performance tests listed in your meeting package the following performance tests should also be completed:

a. Activation Force of the pen injector.

b. Break loose / Glide Force testing for the PFS.
Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf) for more details.

Discussion to CDRH Comments:

None.

Question 11:

Pfizer plans to submit clinical study datasets in the CDISC format following:

- *The Study Data Tabulation Model (SDTM) Version 1.4 implemented using guidance from Version 3.2*
- *The Analysis of Data Model (ADaM) Version 2.1 implemented using guidance from Version 1.1*
- *Study data definitions for both SDTM and ADaM Version 2.0*

Does the Agency agree with this approach?

FDA Response to Question 11:

Yes. Submit sufficiently detailed define files and a reviewer's guide to facilitate understanding and navigation of the datasets, as well as programs for all key efficacy analyses in comparative clinical study B5381002. In particular, if the programs include any SAS macros for efficacy analyses or derivation of analysis datasets from tabulation datasets, provide all necessary macro programs with adequate documentation so that we can independently replicate the efficacy analyses and derive analysis datasets.

Discussion to Question 11:

None.

CMC 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 351(k) BLA submission.

All facilities should be registered with the FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the

BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur (b) (4) (b) (4) The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

b. Bioburden and endotoxin data obtained during manufacture of (b) (4) (b) (4) lots (3.2.S.2.5).

c. Microbial data (b) (4) should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

d. (b) (4) study protocols and acceptance criteria for bioburden and endotoxin samples. (b) (4) (3.2.S.2.5).

e. Information and summary results from the shipping validation studies (3.2.S.2.5).

f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).

g. Summary reports and results from bioburden and endotoxin test method qualification studies performed for (b) (4) the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 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. Identification of the manufacturing areas and (b) (4) including area classifications.

b. Description of the (b) (4) acceptance criteria.

c. Parameters for filling and plunger placement for the pre-filled syringes.

d. Parameters for filling and capping for the vials.

e. A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

f. (b) (4)

g. Sampling points (b) (4) for bioburden and endotoxin. (b) (4)

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

a. (b) (4) Include a comparison of validation test parameters with routine (b) (4) parameters.

b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.

c. (b) (4) Bioburden and endotoxin levels (b) (4) should be monitored and bioburden and endotoxin limits provided.

d. (b) (4) summary data and information, if applicable.

e. Three successful [redacted] (b) (4) including summary environmental monitoring data obtained [redacted] (b) (4) Describe the environmental and personnel monitoring procedures [redacted] (b) (4) and compare them to the procedures followed during routine production.

f. Information and summary results from shipping validation studies. For prefilled syringes, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.

g. Validation of vial capping parameters, using a container closure integrity test.

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

h. Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
i. Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

j. Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b). In accordance with 21 CFR610.9, an alternative pyrogen test may be submitted *in lieu* of the rabbit pyrogen test (such as a Monocyte Activation Test). Full supporting test validation data should be submitted to support the use of a non-compendial pyrogen test.

k. Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. The effect of hold time on endotoxin detection should be assessed by spiking a known

Discussion for CMC Microbiology Comments:

The Sponsor presented the DS and DP Shipping Validation strategy and studies (refer to slides 13-15 of attachment). There was a discussion between the Sponsor and Agency regarding shipping validation requirements for the BLA submission. The BLA should contain data supporting DS shipping under worse case situations in either passive or active containers. In addition, syringe shipping validation studies should include container closure integrity testing

and plunger movement studies to verify the maintenance of the container closure integrity and hence sterility of the product after shipment.

The Sponsor also provide information for intermediate hold time validation, manufacturing process flow, and PV/PPQ challenge strategy (refer to slides 16-20). The Agency conveyed to the Sponsor (b) (4)

Additional discussion: The Sponsor confirmed that they plan to include the following presentations in the original submission: prefilled syringe (40 mg/0.8 mL, 20 mg/0.4 mL, and 10 mg/0.2 mL), prefilled pen (40 mg/0.8 mL), and vial (40 mg/0.8 mL). The Agency inquired if the final to-be-marketed products were used in the clinical studies. The Sponsor noted that the products used in the clinical studies were manufactured using the same process as the to-be-marketed product. The sponsor further clarified that no changes in pre-filled syringe product were made compared to the clinical batches and minor modifications were introduced to the to-be-marketed auto-injector product compared to that used in clinical studies. The Agency recommended that any differences between the products used in the clinical studies and the to-be-marketed products should be bridged or adequately justified. Whether the bridge or justification are adequate will be a review issue.

Post-Meeting Comment: The Agency's preliminary view regarding the Sponsor's plan to submit data to support licensure of a 10 mg/0.2mL PFS presentation in the original BLA is that the plan is acceptable. However, the Agency's preliminary view may change based on further information provided by Pfizer and as the Agency's thinking evolves on certain statutory provisions, including those regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  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.

- 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/Guida

ces/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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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).

In addition, you should review the draft FDA Guidance for Industry, "Labeling for Biosimilar Products," March 2016 at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). 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.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached for the Sponsor's meeting discussion/agenda slides.

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

/s/

JESSICA K LEE
07/12/2018