CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761140Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118281

MEETING MINUTES

Amgen, Inc.
Attention: Renee Martin, PhD
Senior Manager, Global Regulatory Affairs, Biosimilars
601 13th Street NW, Suite 1100 North
Washington, DC 20005

Dear Dr. Martin:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABP 798.

We also refer to the meeting between representatives of your firm and the FDA on November 20, 2019. The purpose of the meeting was to reach agreement on the content, structure, and format of the proposed Biologics License Application (BLA) for ABP 798 as a biosimilar candidate to rituximab and to discuss the key aspects of product quality, nonclinical, and clinical content of the submission.

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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Clinical Team Leader (Acting)
Division of Hematologic Malignancies 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: November 20, 2019; 9:00 AM – 10:00 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 118281
Product Name: ABP 798
Indication: The same indications as approved for US-licensed Rituxan
Sponsor Name: Amgen, Inc.

Meeting Chair: Nicholas Richardson, MD
Meeting Recorder: Beatrice Kallungal, MS

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies 2
Nicole Gormley, Director (Acting)
Nicholas Richardson, DO, MPH, Clinical Team Leader (Acting)
Margaret Merino, MD, Clinical Reviewer
Beatrice Kallungal, MS, Senior Regulatory Project Manager

OOD/Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD, Reviewer

Office of Biostatistics (OB)/Division of Biometrics IX
Jingjing Ye, PhD, Team Leader
Wenjuan (Jessie) Gu, PhD, Reviewer

Office of Drug Evaluation II/ Division of Pulmonary, Allergy, and Rheumatology Products
Nikolay Nikolov, MD, Associate Director for Rheumatology
Raj Nair, MD, Clinical Team Leader (Acting)
Stefanie Freeman, MD, Clinical Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology II
Ping Ji, PhD, Team Leader
Lei He, PhD, Reviewer
Salaheldin Hamed, PhD, Reviewer

OB/Division of Biometrics III
Rebecca Rothwell, PhD, Team Leader (Acting)
Cesar Torres, PhD, Reviewer

Office of Biotechnology Products/Division of Biotechnology Research and Review 1
Marjorie Shapiro, PhD, Lab Chief
Sean Fitzsimmons, PhD, Reviewer
Emanuela Lacana, PhD, Associate Director of Biosimilar Regulatory Policy

Office of Process Manufacturing Assessment/Division of Biotechnology Manufacturing(DBM)
Monica Commerford, PhD, Consumer Safety Officer

Office of New Drugs (OND)/Office of Therapeutic Biologics and Biosimilars
M. Stacey Ricci, MEng, ScD, Acting Director of Scientific Review Staff
Sarah Schrieber, PharmD, Scientific Reviewer
Nina Brahme, PhD, MPH, Scientific Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

David Chien, MD, Medical Director, Biosimilars Global Development
Tracy Dianis, MS, Director, Global Regulatory Affairs, Biosimilars
Gary Fanjiang, MD, MBA, MS, Vice President, Biosimilars Global Development
Renee Martin, PhD, Senior Manager, Global Regulatory Affairs, Biosimilars
Mindy Mo, PhD, Senior Manager, Biostatistics, Biosimilars Development
Jean Pan, PhD, Director, Biostatistics, Biosimilars Development
Melissa Placke, MA, Senior Manager, Global Regulatory Affairs, Biosimilars CMC
Barbara Rellahan, MS, PhD, Director, Product Quality
Neungseon Seo, PhD, Principal Scientist of Process Development, Biosimilars

1.0 BACKGROUND

ABP 798 is a genetically engineered chimeric murine/human immunoglobulin isotype class G subclass 1 (IgG1) monoclonal antibody composed of murine variable regions and human constant regions. The amino acid sequence of ABP 798 is identical to that of rituximab. The sponsor is seeking approval for the same indications that are approved for US-licensed Rituxan. The current approved indications for US-licensed Rituxan (USPI, 2019): Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic lymphoma (CLL), granulomatosis with polyangiitis (Wegener's granulomatosis, GPA), and microscopic polyangiitis (MPA) and pemphigus vulgaris.

Reference ID: 4722550

Amgen is preparing a Biologic License Application (BLA) for ABP 798 as a biosimilar candidate to US-licensed Rituxan (rituximab) to be submitted under Section 351(k) of the Public Health Service (PHS) Act.

The purpose of this requested meeting is to:

- reach agreement that the content of the proposed ABP 798 BLA is appropriate to facilitate the filing and review of the biosimilar candidate to rituximab.
- reach agreement on key aspects of product quality, nonclinical, and clinical content.
- reach agreement on the BLA structure and format.

FDA sent Preliminary Comments to Amgen on November 14, 2019. The Sponsor provided responses to FDA's preliminary comments to facilitate the meeting 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 Amgen 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: *Amgen will submit the agreed initial pediatric study plan (iPSP) as well as the amended iPSP in the original BLA in consideration of new information with respect to the GPA and MPA indications. Does the Agency agree with Amgen's plan and agree to review the amended iPSP during the BLA review cycle?*

FDA Response to Question 1: Given the circumstances here, while the Agency would prefer for the amended iPSP to be submitted as soon as possible, the Agency does not object to your proposed plan for the submission of the amended iPSP with the BLA submission.

Discussion: **No discussion occurred.**

Question 2: *Does the Agency agree that the proposed content, structure, and format of Module 3 will facilitate review of the BLA?*

FDA Response to Question 2: In general, we agree with the proposed content, structure and format of Module 3; however, we have the following recommendations regarding modifications to the content of Module 3:

- 3.2.S.2.4 Controls of Critical Steps and Intermediates: (b) (4)

- 3.2.R Regional Section "Analytical Similarity Assessment": The Draft FDA Guidance for Industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019) states that an "emphasis should be placed on developing orthogonal quantitative methods to definitively identify any differences in product attributes." We note that a single assay (CEX-HPLC) is proposed for the assessment of charge variants. We recommend that you include an additional, orthogonal assay for charge variants or provide sufficient justification for using a single assay.

  The draft guidance also recommends that the stability profile comparisons include studies under multiple stress conditions. In addition to the proposed elevated temperature conditions, we recommend that your comparative analytical assessment also include forced degradation studies such as deamidation, oxidation, agitation, light exposure and freeze-thaw.

  Finally, we note that you propose equivalence testing for analysis of ADCC and CDC data. Although this approach is acceptable, the draft guidance states, "One approach to data analysis would be the use of descriptive quality ranges for assessing quantitative quality attributes of high and moderate risk…" Refer to Section VI.B.2 of the draft guidance for additional details.

- To facilitate the Agency's review of ABP 798 DS and DP manufacturing processes, provide information for all process parameters and controls proposed for routine commercial manufacturing, as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted Module 3.2.R as a single document. Note that these tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT UNIT OPERATION

Process parameter/ operating parameter/In-process control (IPC)/In-process tests (IPT)[1]	Proposed Range for Commercial Manufacturing[2]	Criticality classification[3]	Characterized Range from process development[2]	Manufacture range from historical experience[4]	Manufacture range[5] assessed during process validation	Justification of the proposed commercial acceptable range[6]	Comment[7]

[1]Terminology should be adapted to those used by ABP 798
[2]As applicable.
[3]For example, critical process parameter, non-critical process parameter, as described in Module 3.
[4]Manufacturing experience for the DP lots, and associated DS lots, which were used in the clinical studies to establish product safety and efficacy profile (i.e., pivotal clinical studies).
[5]Operation ranges, not the acceptance criteria, used during process validation.
[6]This could be a brief verbal description (e.g., "development range", "validation range", or "historical manufacturing experience", etc.) or links to the appropriate section of the eCTD.
[7]Optional.

- Refer to the Additional Product Quality Microbiology comments at the end of this document for additional information.

Discussion: **The Sponsor confirmed that the requested summary tables will be provided in the BLA submission. The Agency clarified that the request for the summary tables from OBP is not a requirement and is not specific to ABP 798. The summary tables are being requested for new 351(a) and 351(k) BLAs to facilitate efficient review of the BLA.**

Question 3: *Does the Agency agree that the proposed nonclinical studies will facilitate review of the BLA?*

FDA Response to Question 3: Based on the information provided in the meeting package, the nonclinical studies appear acceptable for the filing and review of the 351(k) BLA for ABP 798. The adequacy of the studies to support the marketing of ABP 798 will be determined during the review of the BLA.

Discussion: **No discussion occurred.**

Question 4: *Can the Agency advise if the clinical study report (CSR) for the PK/clinical similarity Study 20130108 should be placed in Module 5.3.3.2 (Patient PK and Initial Tolerability Study Reports) or Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication)?*

FDA Response to Question 4: The clinical study report for Study 20130108 should be placed in Module 5.3.3.2 (Patient PK and Initial Tolerability Study Reports).

Discussion: **No discussion occurred.**

Question 5: *Does the Agency have any comments or additional points to consider regarding the results from Study 20130108 in the RA population and Study 20130109 in the NHL population to support a demonstration of biosimilarity?*

FDA Response to Question 5: The adequacy of the data from studies 20130108 and 20130109 to support a demonstration of biosimilarity will be a review issue. Since you are seeking the same indications as the reference product, in your application, you will need to provide a justification for the proposal to extrapolate data and information to support licensure as a biosimilar for additional conditions of use.

Regarding study 201308, we have the following comments:

- We refer you to the prior meeting minutes from the meeting 5 April 2017. We have not received your revised SAP for review for study 20130108 and therefore cannot provide additional comments on planned analyses. We expect that the analysis results presented in the submission will reflect the prespecified methods described in the latest version of the SAP finalized prior to the locking of the dataset. Because we have not reviewed this version of the SAP, during the course of our review of your submission, we may ask for additional analyses as Information Requests.

- In particular, we note that you have chosen to continue with your original similarity margin, rather than the (-0.6, 0.5) margin recommended by the FDA. You should include in your submission a justification for continuing to use the wider margin (-0.6, 0.6) in your analyses. While your topline results appear to be within both margins, it is not clear if this difference in margin selection will become relevant for supplementary or additional analyses.

- We note that from prior communications with you, you intend to provide rate ratios along with confidence intervals for Events of Interest (EOIs), as well as descriptive analyses for the incidence of AEs following the second dose. We recommend that you also provide confidence intervals for differences in incidence for AEs, in the comparison of two treatments. Also provide analysis of the impact of ADA results on PK, efficacy and safety both before and after the transition. Submitted datasets should clearly identify patients who undergo a single transition from US-licensed Rituxan to ABP 798 from patients who remain on rituximab for comparative analyses of safety and immunogenicity after the single transition.

Discussion (Study 20130108): **The Sponsor agreed that the analysis of the impact of ADA results on PK, efficacy, and safety before the transition from US-licensed Rituxan to ABP 798 will be presented in the BLA, and that the datasets in the BLA will clearly identify the subjects who underwent the single transition.**

The Sponsor stated that only five subjects (1 in the ABP 798 arm, 3 in the EU-approved MabThera arm, and 1 in the US-licensed Rituxan/ABP 798 arm) developed binding ADAs after week 24. Given this small number of subjects, the Sponsor considered that any analysis of the impact of developing binding ADAs after the transition is not expected to be meaningful.

The Agency clarified that although only five subjects developed binding ADAs after Week 24, it is unclear if the ADA levels (as measured by signal to noise ratio) of subjects who developed binding ADAs before Week 24 have changed after the transition. Therefore, the Agency requested that the impact of ADA status (i.e. ADA positive vs. ADA negative) as well as ADA levels on PK, efficacy, and safety should be assessed before and after the transition. The Sponsor agreed and stated that the PK collection was different for the second period of the study and that the second period only included collection of trough levels. The Agency acknowledged that the PK collection was different, but that an impact analysis conducted with the available PK information should be provided.

Regarding Study 20130109, we have the following comments:

- Clarify whether there is data to support an evaluation of durability of response and the degree of follow up that is available for progression and survival.

- We note the rate of discontinuation to due to AEs was reported in 4 patients (3.1%) who received ABP 798 vs 1 patient (0.8%) who received US-licensed Rituximab. In your submission, include narratives for all subjects who discontinued treatment due to AEs, all SAEs, and any deaths.

Discussion (Study 20130109): **The Sponsor clarified that the end of study 20130109 was at the week 28 response assessment and no further data was collected following that timepoint. Therefore, there is no data on duration of response or survival outcomes following week 28 and the Agency acknowledged this limitation of the efficacy data.**

Since the Sponsor intends to seek the same indications as previously approved for US-licensed Rituxan, the Agency reiterated that the BLA application must include a justification for extrapolation, which, in part, should be based on the data and information from the conducted clinical studies in patients with RA and FL, to support licensure as a biosimilar for additional conditions of use.

Additional Comments

Statistical Comments for Study 20130109 in the NHL population:

1. We recommend using all randomized subjects in the analysis of the primary endpoint.

2.&We recommend exact binomial method for calculation of rate difference and confidence interval for ORR between the two groups.

Discussion: **The Sponsor clarified that the proposed primary analysis was of a modified ITT which excluded 9 subjects (5 subjects on ABP 798, 4 subjects on the US-licensed Rituxan arm) that did not have evaluable disease per IRC-assessment.**

The Agency recommended that the Sponsor include all randomized subjects in the primary analysis and consider the patients who were determined not to have evaluable disease per IRC as non-responders. The Sponsor agreed to this proposal and will also include additional analyses that include these subjects as responders, non-responders, and evaluations per investigator assessment.

Product Quality Microbiology Comments:

The FDA is 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. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

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:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).

- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

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

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

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

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"*.[2]

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

- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling and capping for the vials.

- 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

[2] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

depyrogenation, including process parameters. The list should include single-use equipment.

- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

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

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

- 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.

- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Isolator decontamination summary data and information, if applicable.

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

- Information and summary results from shipping validation studies.

- Validation of 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:

- 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.

- 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.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

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

- Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours.

Discussion: **No discussion occurred.**

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The proposed content and format of the application, as outlined in the meeting briefing package, appears acceptable to the Agency.

- It was noted that there is an Agreed Initial Pediatric Study Plan (Agreed iPSP) for ABP 798 for the treatment of the same indications as approved for

US-licensed Rituxan. Subsequently, there has been additional indications approved for US-licensed Rituxan, and the Sponsor clarified their plans to include an amended iPSP in the upcoming BLA submission.

- 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 not held as these will ultimately be review issues.

- 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 (PREA) (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, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

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 iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we 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.16 in FDA's draft guidance for industry on New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018). 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 iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov 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)[3] and 201.57[4] 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[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[5] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[6] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- 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*.[7]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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 *Nonproprietary Naming of Biological Products*, 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.

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the cGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection, 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-license inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

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*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:

    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).

    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.

    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) 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.

2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:

    a. Site number

    b. Principal investigator

    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

    d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[8] to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The presentations used during this meeting have been appended to the meeting minutes.

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[8] https://www.fda.gov/media/131425/download

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/

NICHOLAS C RICHARDSON
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