CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761373Orig1s000
761425Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 136959

MEETING PRELIMINARY COMMENTS

Samsung Bioepis Co., Ltd
c/o Biologics Consulting Group, Inc.
Attention: Norman W. Baylor, PhD
U.S. Agent for Samsung Bioepis Co., Ltd
1555 King Street, Suite 300
Alexandria, VA 22314

Dear Dr. Baylor:

Please refer to your pre-investigational new drug application (PIND) file for SB17.

We also refer to your correspondence, dated and received November 21, 2022, requesting a meeting to discuss the format and content of your proposed biosimilar biological product application.

Our preliminary responses to your meeting questions are enclosed.

You should provide an electronic version of any materials to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Craig Johnson, PharmD
Regulatory Project Manager
Division of Regulatory Operations for
Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: January 20, 2023, 9:30 – 10:30 a.m.
Meeting Location: Teleconference

Application Number: PIND 136959
Product Name: SB17

Proposed Indication: SB17 is being developed for the same indications as those approved for US-licensed Stelara

Sponsor Name: Samsung Bioepis Co., Ltd
Regulatory Pathway: 351(k) of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 20, 2023, from 9:30 – 10:30 a.m. between Samsung Bioepis Co., Ltd and the Division of Dermatology and Dentistry. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of meeting:
The purpose of this meeting is to discuss the format and content of your proposed biosimilar biological product application.

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Samsung Bioepis Co., Ltd. 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

2.1. CDER ESUB and eDATA

Question 1:

Samsung requests the Agency's agreement and comments on the following points regarding the content of the SB17 BLA:

a) The core eCTD structure

b) The datasets and dataset standards for the study SB17-1001 and SB17-3001

c) The clinical study program of SB17 consists of two studies – a Phase I study in healthy subjects (SB17-1001) and a Phase III study in subjects with moderate to severe plaque psoriasis. Given the differences between these two clinical studies in terms of study populations, objectives, and treatment regimens, Samsung considers that an integrated summary of effectiveness (ISE) and integrated summary of safety (ISS) narrative summary would not be informative. Therefore, ISE/SS will be placed in CTD Section 2.7, and only a leaf element will be provided in CTD Section 5.3.5.3, which will refer the reviewers to CTD Section 2.7.

d) To include Phase III study (SB17-3001) only in bioresearch monitoring (BIMO)

FDA Response to Question 1:

a) From a technical perspective (and not content related), the planned content on the Table of Contents (core eCTD Structure) is acceptable.

b) From the technical perspective (format standpoint) the proposal for datasets, dataset standards and datasets related documents for the study SB17-1001 and SB17-3001 is acceptable.

c) This is acceptable.

d) This is acceptable.

2.2. Product Quality

Question 2:

Samsung seeks the Agency's agreement on the filing strategy regarding stability data of PPQ DS and DP. The shelf-life of SB17 DS and DP will be claimed based on pilot or clinical phase batches which are representative of commercial batches (refer

to Question 9), and as supportive data, Samsung plans to include (b) (4) month stability data of PPQ DS and DP in the initial BLA or in the delayed submission within 30 days of the BLA.

Does the Agency have any comments with this approach?

FDA Response to Question 2:

Your strategy to support the proposed shelf-life of SB17 drug substance (DS) and drug product (DP) using long-term stability data from the pilot and/or clinical batches is reasonable, provided that the pilot or the clinical batches are fully representative of your commercial batches. DS and DP expiry dating will be based on the actual real time stability data submitted in support of the application. Per ICH Q5C, a pilot-plant scale is considered as the production of the DS or DP by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

However, your plan to provide only (b) (4) months of long-term stability data for PPQ DS and DP in the initial BLA or within 30 days of the BLA submission is not sufficient to support that the stability profiles of the PPQ lots and the pilot/clinical batches are comparable and to leverage the stability data of the pilot/clinical batches to support the shelf life of commercial DS and DP. Adequate stability data under long-term, accelerated, and stressed/forced degradation conditions, should be included in the original BLA submission to demonstrate that the stability profiles of the clinical and pilot materials used to support SB-17 DS and DP shelf-life are comparable to those of the commercial materials. Therefore, to establish confidence in any trends observed in the stability profile, provide at least 6-months of real time stability data for the DS and DP PPQ lots and sufficient stability data under accelerated and stressed/forced degradation conditions that allow comparison of incremental changes in product quality attributes over time.

Refer to *FDA Response to Question 9* for additional recommendation.

Question 3:

The extractables study data of container closure, and leachables study data of PFS DP and vial DP will be included in the BLA. In the initial BLA, Samsung plans to provide 0-month leachables study data. Leachables study samples for 0-month timepoint were previously aged in long-term storage condition for 4 months and 1.5 months for PFS DP and vial DP, respectively, and thus is considered to enable assessment of leachable compounds over a sufficient period of time. Results of further timepoints will be provided during the review if requested by the Agency.

Does the Agency agree with this approach?

FDA Response to Question 3:

All available data from extractable and leachable studies, including the 4-month leachable results for PFS DP and 1.5-month leachable results for vial DP, should be included in the initial BLA submission for assessment of the impact of potential leachables from the DP container closure system on product quality and patient safety. Additional leachable study results at different time point(s) may be requested during the BLA review cycle. Include a leachable study protocol for evaluating leachables from the container closure system and their impact on product quality and patient safety at the end of shelf life in your post-approval DP stability protocols (for both PFS and Vial presentations).

Evaluation of leachables from the DS and DP manufacturing processes as well as the DS container closure system should also be included in the initial BLA submission.

Question 8:

Samsung seeks the Agency's comments on the preliminary manufacturing schedule for the SB17 DS and DP which is (b) (4) months after the submission of the BLA, in support of the pre-license inspection (PLI).

FDA Response to Question 8:

The drug substance manufacturing schedule is acceptable. We agree that the 90 mg PFS process is representative of the 45 mg PFS process and inspecting only the 90 mg PFS and the vial process is acceptable. However, we recommend scheduling the drug product manufacturing (b) (4) months after the submission to provide sufficient time to review the submission and to arrange the foreign inspection.

Question 9:

For the SB17 BLA, Samsung plans to claim the shelf-life of SB17 DS and DP (PFS and vial) as follows:

a) Samsung intends to claim the shelf-life of SB17 DS as (b) (4) months, based on the real-time long-term stability data of three clinical phase batches available during the BLA review cycle.

b) Samsung intends to claim the shelf-life of SB17 PFS DP (45 mg, 90 mg) as 24 months, based on the real-time long-term stability data of three clinical phase batches and functional stability data of three PPQ batches under accelerated condition available during the BLA review cycle. To support the shelf-life claim of SB17 PFS, accelerated aging factor (AAF) estimation will be

applied to the accelerated functional stability data according to the ASTM guideline.

c) Samsung intends to claim the shelf-life of SB17 vial DP (130 mg) as (b) (4) months, based on 9 months long-term stability data of three PPQ batches available during the BLA review cycle plus additional 6 months based on the comparability between the pilot and PPQ batches.

Does Agency agree or have any comments?

FDA Response to Question 9:

Per ICH Q5C, the assigned shelf-life for DS and DP will be based on the actual stability data under long-term storage conditions provided in the BLA and other relevant data and information, such as comparability assessments and the container closure system.

To support your proposed dating period for SB17 DS and DP, during the BLA review cycle you may provide a "simple stability update" which is defined as follows: stability data and analyses performed under the same conditions and for the same DS and DP batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update should use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and should not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA. Simple stability updates should be submitted to the BLA as soon as possible and no later than month 7 from the initial submission of a 351(k) BLA to be considered in shelf-life determination.

Question 10:

Media fill validation study has been performed (b) (4) at the SB17 DP manufacturing site on the (b) (4) for the PFS and the vial presentation. For the initial BLA, Samsung plans to provide the detailed (b) (4) (b) (4) and the media fill validation results.

Does the Agency have any comments?

FDA Response to Question 10:

You may provide 3 successful media fills (b) (4) (b) (4) Include at least one media fill with the container closures intended for commercial distribution (one for the vial and one for the PFS).

2.3. Clinical

Question 4:

Samsung plans to submit the BLA with complete quality, non-clinical, and Phase I PK data in healthy subjects. From the Phase III study in moderate to severe PsO patients, the full set of 40-week data (including efficacy, safety, tolerability, PK, and immunogenicity data) together with 52-week data from a subset of patients (approximately 103 patients) will be available at the time of BLA submission, with a commitment to submit the full 52-week data of the Phase III study during the BLA procedure at 120-day safety update (refer to Question 5). Results available to date showed that the primary efficacy endpoint, percent change from baseline in PASI at Week 12, met the pre-defined equivalence margin, and that the safety profiles were comparable between SB17 and Stelara. Provided that the full set of 40-week data together with 52-week data from a subset of patients is available at the time of BLA submission and no important safety signals are found, Samsung believes that this interim data is sufficient for the Agency's review of the SB17 BLA.

Does the Agency agree with this approach?

FDA Response to Question 4:

Your proposal appears reasonable. However, the filing determination will be made within 60 days of the BLA submission. The adequacy of the data will be determined during the review of the BLA.

Submit the final bioanalytical report in your initial BLA submission.

All data that you intend to rely on for approval should be included in the application at the time of original submission. Also see the *FDA response to Question 5.*

Question 5:

Samsung would like to submit below information at the time of 120-day safety update.

- Updated CTD section 2.7.4
- Final CSR of Phase III study (SB17-3001) and its dataset
- Updated BIMO

Does the Agency agree with this approach or have any comments?

FDA Response to Question 5:

It is acceptable to include an update to section 2.7.4 (Summary of Clinical Safety) in the 120-day safety update (SU). Although submission of the final study report for the comparative clinical study (SB17-3001) may go beyond the scope of the intent of the

SU, your proposal is acceptable because you will also specifically update section 2.7.4 of the application, the Summary of Clinical Safety. It is acceptable to include updated Bioresearch Monitoring (BIMO) information in the SU.

Question 6:

Samsung acknowledges that a REMS was not required for the reference product, Stelara in the US. SB17 is a proposed biosimilar product having ustekinumab as the active substance, and comprehensive similarity assessment data including quality, non-clinical, clinical Phase I, and clinical Phase III studies will be included in the BLA package to demonstrate high similarity to US Stelara. Accordingly, Samsung believes that there is no need to propose a REMS for SB17 including a medication guide, as well.

Samsung seeks the Agency's advice on the proposed approach in support of a BLA.

FDA Response to Question 6:

We agree that the inclusion of a proposed REMS will not be necessary. The same risk mitigation strategies that are currently in place for the reference product will also apply to the biosimilar. The reference product, US-licensed Stelara, currently does not require a REMS. A Medication Guide is part of patient labeling for US-licensed Stelara and includes information that would be relevant to your biosimilar product. Therefore, include a Medication Guide in the application for SB17.

Question 7:

With regards to the indications, PsO and PsA, while the reference product Stelara is licensed for the use in both pediatric and adult patients, Samsung plans to claim the indications and usage of SB17 for only adult PsO and PsA. Therefore, dosage and administration information of pediatric PsO and PsA will be excluded from the SB17 PI.

Does the Agency agree with this approach or have any comments?

FDA Response to Question 7:

You intend to label your product "for adult therapeutic indications" at initial BLA submission. In the prescribing information, you propose to retain language pertaining to pediatric use from the following sections of the package insert for the reference product, US-licensed Stelara:

a. 6 Adverse reactions: 6.1 Clinical trial experience for pediatric subjects with plaque psoriasis
b. 8.4 Pediatric use

c. 12 Clinical pharmacology: Specific populations – pediatric population under 12.3

d. 14 Clinical studies: 14.2 Adolescent subjects with plaque psoriasis

Your proposal to seek licensure for fewer indications than those for US-licensed Stelara is acceptable[1]. The presentation of information for non-approved indications should avoid implied claims. Labeling decisions will be made during the application review.

You state that you intend to seek only the adult indications for PsO and PsA at the time of initial BLA (b) (4) (b) (4) We remind you that under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Under section 505B(I) of the FD&C Act, 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 generally required unless waived or deferred or inapplicable. Therefore, address PREA (b) (4)

Additional Chemistry Manufacturing and Controls (CMC) 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.

[1] FDA, 2020, Draft Guidance for Industry: Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has been Licensed, https://www.fda.gov/media/134932/download

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 prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

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

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

d. Chromatography resin and UF/DF membrane lifetime study protocols and 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).

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

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

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

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 type of fill line (e.g., open, RABS, isolator), including area classifications.

b. Description of the sterilizing filter (size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study (if the product is sterile-filtered using a pump, pressure upstream the sterilizing filter should be monitored); wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test 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. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

g. 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:

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

d. Isolator decontamination summary data and information, if applicable.

e. 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.

f. Information and summary results from shipping validation studies. 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 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:

a. Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe should be included. 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.

b. 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.

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

d. 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.

e. 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. We recommend periodic intermediate sample times. 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.

3.0 ADMINISTRATIVE LANGUAGE

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA III. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at FDA.gov.[2]

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),

[2] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

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 additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

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 guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. 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)[4] and

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm

201.57[5] 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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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

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mpaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_ca
mpaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm 084159.htm

[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

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*.[8]

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.

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.

STUDIES IN HUMANS MAY NOT BE CONDUCTED UNDER THIS PIND

Before you may conduct studies in humans, you must submit a full Investigational New

[8] 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.

Drug Application (IND, see 21 CFR Part 312[1]) by amending this PIND with the required information. Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND. Send your IND submission in eCTD format through the ESG. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov[9].

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*.

[9] http://www.fda.gov/ectd

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/s/

CRAIG H JOHNSON
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