CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761398Orig1s000
761398Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 145897

MEETING MINUTES

Fresenius Kabi SwissBioSim GmbH
C/O Fresenius Kabi USA
Attention: Shobana Navayath, PhD
Senior Director, Regulatory Affairs Lead
Three Corporate Drive
Lake Zurich, IL 60047

Dear Dr. Navayath:

Please refer to your Pre-Investigational New Drug Application (PIND) file for FKS518.

We also refer to the video conference between representatives of your firm and the FDA on January 23, 2024. The purpose of the meeting was to discuss content, structure, and format of a complete application for the proposed indication(s) and presentations, manufacturing schedules and necessity of pre-license inspection, labelling content and concept, interchangeability status for all the development presentations, and compliance with 21 CFR for the non-IND studies.

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

If you have any questions, call Noreen Cabellon, Regulatory Project Manager at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Shivangi Vachhani, MD
Clinical Team Lead
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biological Product Development (BPD) Type 4
Meeting Date and Time:	January 23, 2024, 10:00 AM to 11:00 AM EST
Meeting Location:	Videoconference
Application Number:	PIND 145897
Product Name:	FKS518
Indication:	FKS518 is being developed for the same indications as those approved for US-licensed Prolia (US-Prolia) and US-licensed Xgeva (US-Xgeva)
Sponsor Name:	Fresenius Kabi SwissBioSim GmbH
Regulatory Pathway:	351(k) of the Public Health Service Act
Meeting Chair:	Shivangi Vachhani, MD
Meeting Recorder:	Noreen Cabellon, MS

FDA ATTENDEES

Office of New Drugs (OND)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

Division of General Endocrinology

Olivia Easley, MD, Clinical Reviewer
Shivangi Vachhani, MD, Clinical Team Lead
Theresa Kehoe, MD, Director

Division of Pharm Tox for Cardiology, Hematology, Endocrinology, and Nephrology

Sree Rayavarapu, PhD, Nonclinical Reviewer
Daniel Minck, PhD, Nonclinical Team Lead
David Carlson, PhD, Nonclinical Supervisor

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology

Hebing Liu, PhD, Clinical Pharmacology Reviewer
Li Li, PhD, Clinical Pharmacology Team Lead

OTS/Office of Biostatistics

Kyunghee Song, PhD, Biometrics Reviewer
Feng Li, PhD, Biometrics Team Leader

Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis
Yevgeniya Kogan, Safety Evaluator Team Lead
Oluwamurewa Oguntimein, Human Factors Team Lead
Division of Risk Management
Theresa Ng, PharmD, Senior Risk Management Analyst
Yasmeen Abou-Sayed, PharmD, RPh, Team Lead

OSE/Immediate Office/Project Management Staff
Deveonne Hamilton-Stokes, RN, BSN, MA, Safety Regulatory Project Manager

Office of Therapeutic Biologics and Biosimilars
Raquel Tapia, M.D., Scientific Reviewer
Nina Brahme, Ph.D., M.P.H., Scientific Reviewer
Shelley Skibinski, Pharm.D., Project Coordinator
Jessica Tyson, PhD, MPH, RAC, Science Policy Analyst
Angela LaPier, J.D., Regulatory Counsel
Hyon Kim, PharmD, BCPS, PMP, Labeling Reviewer
Chau Nguyen, Pharm.D., Project Manager
Emanuela Lacana, PhD, Deputy Director

OND/Office of Oncologic Diseases (OOD)
Division of Oncology I
Gwynn Ison, MD, Clinical Reviewer
Daniel Suzman, MD, Deputy Division Director

Office of the Commissioner (OC)/Office of Clinical Policy and Programs (OCPP)/Office of Combination Products (OCP)
Bindi Nikhar, MD, Associate Clinical Director

Office of Compliance/Office of Scientific Investigations
Division of Clinical Compliance Evaluation
Ling Yang, MD, PhD, Medical Officer

OND/Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Noreen Cabellon, MS, Regulatory Project Manager
Elisabeth Hanan, MS, Chief, Project Management Staff

SPONSOR ATTENDEES
Shobana Navayath, Senior Director, Regulatory Affairs
Akansh Dixit, Senior Manager, Regulatory Affairs
Marine Revol, Senior Director, Global Program Management
Kriti Shukla, Senior Manager, Global Program Management

Fabrice Heitz, Principal Scientist, Nonclinical Pharmacology
Damjan Rajapakse, Senior Manager, Physicochemical CMC Development
Antoine Boulet, Director, Medical Device
Peter Szeles, Senior Manager, Clinical Affairs
Amel Besseghir, Senior manager, Statistical Programming, Clinical Development, Medical & Pharmacovigilance
Satish Ghadigaonkar, Senior Manager, Biostatistics, Clinical Affairs, Safety and Medical Affairs

1.0 BACKGROUND

Fresenius Kabi SwissBioSim GmbH (Fresenius) is developing FKS518 for the same indications as those approved for US-licensed Prolia (US-Prolia) and US-licensed Xgeva (US-Xgeva).

An initial BPD Type 2 meeting with Fresenius to discuss the FKS518 development program was held on February 13, 2020, and meeting minutes were issued on March 13, 2020. Written responses were issued for subsequent BPD Type 2 meeting requests which addressed Fresenius's questions regarding the results of the validation of the pharmacokinetic (PK), anti-drug antibody (ADA) and neutralizing antibody (Nab) assays before the start of the clinical study sample analyses (June 2, 2021); the proposed development program regarding the chemistry, manufacturing, and controls (CMC) and combination drug device aspects for FSK518 (October 26, 2021); and the proposed statistical analysis plan for FKS518-002 (Luminade-3)[1] and to confirm that the proposed estimands and statistical analyses are acceptable to demonstrate equivalent efficacy of FKS518 (September 26, 2022).

A BPD Type 2b meeting with Fresenius was held on July 17, 2023, to discuss aspects of quality and submission strategy. In a post meeting comment in the August 16, 2023, issued meeting minutes, FDA recommended that the Sponsor submit a BPD Type 2a meeting request for input and feedback on the statistical analysis plan (SAP) for the comparative clinical study. FDA granted the BPD Type 2a meeting on September 5, 2023. A written response was issued on October 27, 2023, wherein FDA noted that Fresenius's proposed statistical analyses appeared acceptable.

On November 14, 2023, Fresenius requested this BPD Type 4 meeting to discuss content, structure, and format of a complete application for the proposed indication(s) and presentations, manufacturing schedules and necessity of pre-license inspection, labelling content and concept, interchangeability status for all the development presentations, and compliance with 21 CFR for the non-IND studies. The meeting package was received on November 27, 2023.

[1] A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia in Postmenopausal Women with Osteoporosis

FDA sent Preliminary Comments to Fresenius on January 19, 2024. On January 22, 2024, the Sponsor provided via email a slide presentation for the meeting. The sponsor slide presentation is appended at the end of this document.

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 Fresenius 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

The Sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), and the meeting discussion (bolded/italicized). Post-meeting comments, where applicable, appear after the meeting discussion (underlined).

2.1. Regulatory

Question 1: First Interchangeable Exclusivity (FIE). Denosumab reference products are licensed in the US as Prolia® (60 mg/mL) in a pre-filled syringe (PFS) presentation and Xgeva® [120 mg/1.7 mL (70 mg/mL)] in a vial presentation. The sponsor has developed a 60 mg/mL PFS presentation similar to US-Prolia and a 70 mg/mL vial presentation similar to US-Xgeva. The sponsor has also developed an additional PFS presentation with the same strength as that of US-Xgeva (70 mg/mL) vial presentation. The sponsor intends to seek licensure as an interchangeable biosimilar for all the FKS518 presentations i.e., 60 mg/ mL PFS and 70 mg/ mL vial and PFS.

The Food and Drug Omnibus Reform Act (FDORA) made changes to the Public Health Services Act (PHS Act) that "when a subsequent application for an interchangeable product is blocked by the First Interchangeable Exclusivity (FIE), FDA can approve that application as a biosimilar" [Regulatory Education for Industry (REdI) Annual Conference 2023].

a) The Sponsor is of the understanding that if approval of FKS518 as an interchangeable is blocked by FIE, then, in such a scenario FKS518 will be approved as a biosimilar to the originator products Prolia and Xgeva (subjective to the BLA review by the USFDA) even if the Sponsor has requested for approval as an interchangeable biosimilar in the initial BLA. Does the Agency confirm the Sponsor's understanding?

b) If the Sponsor's understanding in "Question 1a" is confirmed by the Agency, the Sponsor will mention the above understanding (described in Question 1a) in the cover letter submitted along with the initial BLA. Does the Agency have any other procedural prerequisites to fulfil such requests?

c) If the Agency validates "Question 1a," the Sponsor's viewpoint is that upon the expiration of the First Interchangeable Exclusivity (FIE), FKS518 could potentially achieve approval as an interchangeable biosimilar (granted all requirements are met) without the submission of an sBLA. Does the Agency concur with the proposed approach? Or are there any additional procedural requirements to gain approval as interchangeable?

d) FKS518 70 mg/mL has a prefilled syringe presentation for which the originator Xgeva is not licensed. The Sponsor would like to know whether the novel PFS presentation also will be blocked by FIE, even if the first interchangeable biosimilar approved in the US does not have this presentation?

FDA Response to Question 1a: **If an applicant indicates in its cover letter that a BLA submitted under section 351(k) contains information intended to demonstrate interchangeability, the Agency generally plans to evaluate the BLA as both an application for licensure of a biosimilar product and an application for licensure of an interchangeable biosimilar. In such cases, if a BLA submitted under section 351(k) contains data and information sufficient to support licensure of the product as an interchangeable biosimilar, but approval may not be made effective by FDA until the expiration of an applicable period of exclusivity, FDA may split the application for administrative purposes. This would enable the Agency to take separate actions on such a BLA as appropriate.**

FDA Response to Question 1b: **No.**

FDA Response to Question 1c: **It would be premature for FDA to respond to this question. If this situation arises, FDA will provide instructions at that time.**

FDA Response to Question 1d: **The response to this question depends on multiple factors. Given the hypothetical nature of this question, it is not possible for us to provide a definitive answer, and it would not be advisable or helpful for us to speculate. For information regarding FDA's determinations relating to first interchangeable exclusivity, please refer to the Purple Book on FDA's website.[2]**

Discussion: ***No discussion occurred.***

Question 2: (b) (4) Claim

a) The Sponsor intends to claim (b) (4) (b) (4)

[2] https://purplebooksearch.fda.gov/

i) The Sponsor would like to claim [redacted]

ii) In case of possibility of a [redacted]

b) [redacted]

c)

FDA Response to Question 2a: **FDA is discussing this question internally. A response will be provided when one is available.**

FDA Response to Question 2b: **See the response to Question 2a.**

FDA Response to Question 2c: **See the response to Question 2a.**

Discussion: [redacted]

(b) (4)

Post Meeting Comment:
Regarding Question 2a, FDA is continuing to consider the issues raised by your question and plans to provide additional comments in a post-meeting communication.

Question 3: USPI development for novel PFS presentation. The reference products US-Prolia® (60 mg/mL) and US-Xgeva® (70 mg/mL) are licensed in the US as pre-filled syringe (PFS) and vial presentations, respectively. In addition to the development of presentations similar to the originator, the sponsor has also developed a prefilled syringe with the strength of Xgeva (70 mg/mL).

The Sponsor will develop a standalone USPI for the 60 mg/mL PFS presentation (similar to that of Prolia). The Sponsor does not intend to develop two separate USPIs but plans to develop a single USPI for both the presentations of FKS518 70 mg/mL [i.e., vial (similar to originator) and PFS (novel presentation)]. Does the agency agree with the proposed approach?

FDA Response to Question 3: **The proposed approach is acceptable.**

Discussion: ***No discussion occurred.***

Question 4: Overall labelling content and concept. Does the Agency have any recommendations on the labeling concept and content for FKS518 based on FDA Guidance for Industry – Labeling for Biosimilar and Interchangeable Biosimilar Products (September 2023), to support 351(k) BLA submission?

FDA Response to Question 4: **Some aspects of the proposed labeling will be dependent on the answer to Question 2. We note that the FDA approved labeling for Prolia does not include Instructions for Use, and the FDA approved labeling for Xgeva does not include Instructions for Use or a Medication Guide. Detailed comments to your proposed labeling will be provided during the BLA review.**

Discussion: ***The Sponsor requested additional clarification via submitted slides. Refer to attached slide 5. The Sponsor inquired if the FDA agreed with the submission of a*** (b) (4)

(b) (4)

Post Meeting Comment:
Regarding seeking licensure of the proposed FKS518 120 mg/1.7 mL (70 mg/mL) PFS for (b) (4), FDA is continuing to consider the issues raised by your question and plans to provide additional comments in a post-meeting communication.

Question 5: Content and format of BLA. Does the FDA have any feedback or recommendations regarding the proposed content and format of FKS518 351(k) BLA as presented in Table of Contents?

a) Does FDA agree that the proposed documents and their location in various CTD modules are considered adequate and sufficient for review? The applicant seeks Agency's advice in case there are additional documents required.

b) Does the Agency have additional comments on the adequacy of the proposed structure of the BLA to support the review?

FDA Response to Question 5a: **We have following recommendations regarding the proposed content and format of FKS518 351(k) BLA:**

1. Many factors, including nutritional factors, which may vary between populations, can impact bone health. Therefore, the sensitivity of the

clinical study may vary between geographic populations. Since a non-US population was enrolled in your comparative clinical study (study FKS518-002), comment on whether the BMD response to the study drugs was similar to the BMD response observed in prior efficacy studies of the reference product. This commentary can be incorporated into the FKS518-002 complete study report in Module 5.3.5.1.

2. **In Module 2.5 Introduction, discuss the data and information that supports extrapolation and licensure for each of the indications being sought and for which US-Prolia and US-Xgeva have been previously approved.**

3. **For both studies FKS518-001[3] and FKS518-002, submit narratives and case report forms for serious adverse events and adverse events leading to premature discontinuation. These can be included in the respective study reports in Modules 5.3.3.1 and 5.3.5.1.**

4. **The proposed content of Module 3 appears acceptable for filing of BLA. Note that 3.2.P.5.2 C Analytical Procedures – Polysorbate 20 Content and 3.2.P.5.2 D Analytical Procedures – Device Performance Tests should be included in folder 3.2.P.5.2 Analytical Procedures (PFS), and an agreement on analytical methods included in sections 3.2.S.4 and 3.2.P.5 will be a review issue.**

Please see additional Clinical Pharmacology comments below for recommendations for formatting of clinical pharmacology information.

FDA Response to Question 5b: **Please see additional Chemistry, Manufacturing, and Controls (CMC) and CMC Microbiology comments below (under Additional FDA Comments) for additional considerations in the BLA.**

Also, if the needle in your device constituent is co-packaged, please add the 510K#.

Discussion: ***The Sponsor requested additional clarification via submitted slides. Refer to attached slides 6, 7, and 8. The Sponsor inquired if the approach to present the detailed information and justification for extrapolation of indications in Module 5.3.5.4 Other Study Reports and Related Information was acceptable. The Sponsor also inquired if the commentary regarding BMD response was acceptable to be included in Module 2.5 Clinical Overview section of the BLA. FDA responded that both these approaches are acceptable.***

[3] FKS518-001 (Lumiade-1) is titled A Double-Blind, Randomized, 2-arm, Single-Dose, Parallel-Group Study in Healthy Subjects to Compare the Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of the FK Proposed Denosumab Biosimilar (FKS518) with the US-licensed Prolia

Lastly, the Sponsor inquired if a draft REMS document was required at the time of the initial BLA submission or if it could be provided during or after BLA review, and whether the plan to develop a stand-alone REMS for the Prolia biosimilar was acceptable. FDA responded that a stand-alone REMS is acceptable. REMS are required for approval but not for filing. FDA further noted that the recent update to the Prolia labeling affected the Prolia REMS and so the updated Prolia REMS will be useful to reference when the Sponsor drafts their REMS documents.

Question 6: Pre-License Inspection. The Sponsor plans to provide the tentative manufacturing schedule options for FKS518 DS and FKS518 DP (for all presentations) in the initial BLA (iBLA) to support pre-license inspection (PLI) 4-5 months after iBLA submission. The manufacturing schedule will be aligned to support FDA PLI.

a) Does the Agency agree that providing tentative manufacturing schedule in the iBLA will meet the needs of the Agency and that the exact schedule can be confirmed closer to the PLI time?

b) Can the Agency confirm they will communicate necessity, scope, and timing for PLI ≥ 60 days in advance of the pre-license inspection and will communicate the need for inspection no later than mid cycle in accordance with the commitments outlined in BsUFA III engagements?

FDA Response to Question 6a: **Yes, a tentative manufacturing schedule can be submitted at the time of the initial BLA submission, and the exact schedule can be confirmed when the manufacturing facility is notified for the pre-license inspection(s) (PLI). Please note that providing the exact manufacturing schedule prior to the midcycle will facilitate inspection planning.**

FDA Response to Question 6b: **Communications with facilities regarding PLI are initiated in advance, prior to midcycle and with the goal of > 60 days prior to an inspection. However, FDA reserves the right to conduct manufacturing facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect. PLIs typically have the scope of pre-license evaluation of the manufacture and testing of the subject product of the BLA according to CGMP, raw materials control, contamination and cross-contamination control, and the quality management system of the facility.**

Discussion: ***No discussion occurred.***

Question 7: Compliance to 21 CFR 312.120 for non-IND studies. FKS518 comparative PK study in healthy volunteers (Lumiade-1) and comparative safety and

efficacy study in patients (Lumiade-3) are foreign studies not conducted under an IND.

a) The Sponsor will demonstrate compliance to 21 CFR 312.120(b) in the BLA for the above 2 clinical studies. The supporting information to show compliance to 21 CFR 312.120(b) will be provided in Module 5, Section 5.2 Tabular Listing of All clinical Studies. Does the Agency agree to the proposed approach?

b) Since, both the clinical studies i.e., comparative PK and comparative safety and efficacy studies for FKS518 are non-IND studies, the Sponsor is of the understanding that a specific Transfer of Regulatory Obligations (TORO) document, ordinarily submitted in respect of IND studies between the Sponsor and the Contract Research Organisation (CRO) will not be required in Module 1, Section 1.3.1.4 Transfer of Obligations. Does the Agency agree with the approach?

c) The Sponsor will instead provide, in the BLA, a table detailing the full list of activities transferred to the CRO with respect to the non-IND comparative clinical PK and safety and efficacy studies under Module 1, Section 1.3.1.4 Transfer of Obligations. Does the Agency concur with the proposed approach?

FDA Response to Question 7a, b, and c: **Your approaches appear acceptable for the PK similarity study and the comparative safety and efficacy study. Please note that as a sponsor, you may transfer any or all of your study-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the study data always resides with the sponsor.**

Discussion: ***No discussion occurred.***

Question 8: Summary of Clinical Safety and Summary of Clinical Efficacy. Does the Agency concur that a formal integrated/pooled safety data analysis can be waived, considering the different populations [i.e., Healthy volunteers (HVs) and women with PMO] and study designs of the two clinical studies to be included in the planned BLA, while safety results can be presented comprehensively in the Summary of Clinical Safety (Module 2.7.4)? An Integrated Summary of Efficacy (ISE) is not planned to be provided in the BLA as there is only one efficacy study in the FKS518 clinical program. Does the Agency concur that the Summary of Clinical Efficacy (Module 2.7.3) can serve as the Integrated Summary of Efficacy (ISE)?

FDA Response to Question 8: **The Agency concurs that the SCS and SCE are sufficient and integrated summaries are not required based on the disparate study designs and populations.**

Discussion: ***No discussion occurred.***

Additional FDA Comments

Chemistry, Manufacturing, and Controls (CMC):

1. **To facilitate our review of the drug substance (DS) and drug product (DP) manufacturing processes for FKS518, provide the information for process parameters and in-process controls, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.**

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/ Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/ Targets[1] tested in Process Development Studies	Manufactured Range/ Targets[1] used for Clinical Study Lots	Manufactured Range/ Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1]As applicable.
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[4]Optional.

Note that a submission of the requested information will not replace detailed manufacturing process development, validation, and other relevant information/data in corresponding Module 3 sections (e.g., in 3.2.S.2.6, 3.2.S.2.5, 3.2.P.2, 3.2.P.3.5).

2. **To facilitate our review of the control strategy for FKS518, provide information for quality attributes and process- and product-related impurities for the DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.**

Quality Attributes and Process and Product Related Impurities for DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[5]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.

[6]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[7]Optional.

CMC Microbiology:

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.

3. **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 FDA Establishment Identifier (FEI) numbers. A preliminary manufacturing schedule for the DS and DP 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.**

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

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

      i) **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).**

      ii) **Bioburden and endotoxin data obtained during manufacture of three PPQ lots (3.2.S.2.5).**

      iii) **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).**

      iv) **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).

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

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

vii) 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).

b) 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 FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.[4]

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

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

ii. 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.

iii. Parameters for filling and plunger placement for the pre-filled cartridges.

iv. 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

[4] 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.

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

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

vi. 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.

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

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

ii. 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.

iii. 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.

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

v. 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.

vi. 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.

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

   i. **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 cartridges and pen devices 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.**

   ii. **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.**

   iii. **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.**

<u>Combination Product</u>

5. **The proposed FKS518/denosumab biosimilar biological product that will be provided as a 60 mg and a 120 mg prefilled syringe is a single-entity combination product per 21 CFR 3.2(e)(1). Please note that Part 3 combination products are subject to 21 CFR Part 4.A "Current Good**

Manufacturing Practice Requirements for Combination Products".[5] Please also refer to FDA's guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*. Because your combination product includes a biological product, this includes compliance with the identified cGMP requirements specific to biological products in Parts 600 through 680 (21 CFR Parts 600 through 680).

6. **Form 356h - In your future submissions, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.**

7. **For information on the location of device related information, see Section 5 of FDA's eCTD Technical Conformance Guide: Technical Specifications Document[6] and FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.**

8. **Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see FDA's website.[7]**

***Discussion:* No discussion occurred.**

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
  FDA clarified that applications under the program must be complete at the time of initial 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.

[5] accessible at: https://www.federalregister.gov/documents/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products
[6] accessible at https://www.fda.gov/media/93818/download
[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

- A preliminary discussion regarding the approach to developing the content for a REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions for Use) and, where applicable, the development of a Formal Communication Plan was held and it was concluded that a stand-alone REMS for FKS518 is required for approval but not for filling. The Sponsor should reference the most recent Prolia REMS when drafting the REMS documents.

- 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 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*[8]. 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)[9] and 201.57[10] including the Pregnancy and Lactation Labeling Rule (PLLR). As you develop your proposed PI, we encourage you to review the labeling review resources on the following websites:

- *Biological Products – Specific Labeling Resources*[11] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[12]

For other prescription drug labeling resources such as those for FDA-approved patient labeling, carton and container labeling, labeling databases, and product databases, visit *FDA's Labeling Resources for Human Prescription Drugs* website.[13]

- 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

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[9] 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
[10] 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
[11] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[12] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[13] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

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*.[14]

Prior to submission of your proposed PI, use the Selected Requirements for Prescribing Information (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.

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.

[14] 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.

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 III.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[15] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[16]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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:

[15] https://www.fda.gov/media/84223/download
[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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[17] 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.

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

Discussion: ***The Sponsor requested additional clarification via submitted slides. Refer to attached slide 9. The Sponsor inquired if FDA agreed with their approach to describe data definitions in "define.xml" instead of "define.pdf". FDA responded that this approach was acceptable.***

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

FDA to provide the Sponsor a response to the Sponsor's Question 2 regarding the 120 mg/1.7 mL (70 mg/mL) PFS novel presentation and self-administration claim, and Question 4 regarding the overall labelling content at the time the information is available.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slide presentation provided via email on January 22, 2024, is appended.

9 Page(s) has 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/

SHIVANGI R VACHHANI
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