CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 141802

MEETING MINUTES

Samsung Bioepis Co., Ltd.
C/O Biologics Consulting Group, Inc.
Attention: Norman W. Baylor, PhD, US Agent
President & CEO
1555 King Street, Suite 300
Alexandria, VA 22314

Dear Dr. Baylor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SB16.

We also refer to the teleconference between representatives of your firm and the FDA on September 22, 2023. The purpose of the meeting was to discuss and introduce the planned Biologics License Application (BLA) content and to obtain additional advice on issues related to the content and presentation of the BLA.

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

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, M.D.
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	BPD Type 4
Meeting Date and Time:	Friday, September 22, 2023; 9:00 – 10:00 am EDT
Meeting Location:	Teleconference
Application Number:	IND 141802
Product Name:	SB16
Indication:	SB16 is being developed for the same indications as those approved for US-licensed Prolia and US-licensed Xgeva
Sponsor Name:	Samsung Bioepis Co., Ltd.
Regulatory Pathway:	351(k) of the Public Health Service Act
Meeting Chair:	Olivia Easley, MD
Meeting Recorder:	Jennifer Johnson, Regulatory Health Project Manager

FDA ATTENDEES

Office of New Drugs (OND), Office of Cardiology, Hematology, Endocrinology, and Nephrology, Division of General Endocrinology
Olivia Easley, MD, Clinical Reviewer
Karen Vogt, MD, Clinical Reviewer
Shannon Sullivan, MD, PhD, Clinical Team Leader
Naomi Lowy, MD, Deputy Director
Theresa Kehoe, MD, Director

OND, Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Jennifer Johnson, Regulatory Health Project Manager, Endocrinology
Elisabeth Hanan, MS, Chief, Project Management Staff

Office of Translational Sciences (OTS), Office of Clinical Pharmacology
Li Wang, PhD, Clinical Pharmacology Reviewer
Li Li, PhD, Clinical Pharmacology Team Leader (Acting)

OTS, Office of Biostatistics
Kiya Hamilton, PhD, Biometrics Reviewer
Feng Li, PhD, Biometrics Team Leader

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products
Md Rahim, PhD, Product Quality Assessor
Kelley Burridge, PhD, Product Quality Team Leader

OPQ, Office of Program and Regulatory Operations, Division of Regulatory and Business Process Management 1, Regulatory and Business Process Management Branch 2
Nowrin Kakon, MLS (ASCP), Regulatory Business Process Manager

Office of Scientific Investigations
Ling Yang, MD, PhD, Physician
Min Lu, MD, MPH, Team Lead

Office of Surveillance and Epidemiology, Project Management Staff
Ameet Joshi, PharmD., Team Lead, Project Management Staff
Deveonne Hamilton-Stokes, MA, BSN, RN, Safety Regulatory Project Manager

Office of Surveillance and Epidemiology, Division of Risk Management (DRM)
Theresa Ng, PharmD., Risk Management Analyst
Yasmeen Abou-Sayed Pharm.D., DRM Team Leader
Laura Zendel, PharmD., DRM Associate Director

Office of Surveillance and Epidemiology, Division of Medication Error and Prevention and Analysis 1
Murewa Oguntimein, PhD, MHS, CPH, MCHES, Human Factors Team Lead

Office of Therapeutic Biologics and Biosimilars
Michelle Luo, M.D, Ph.D., Scientific Reviewer
Carol Kim, Pharm.D., Scientific Reviewer
Emanuela Lacana, PhD, Deputy Director
Jacqueline Rosenberger, PharmD, RAC, Senior Project Manager
Wendy Streight, Ph.D., Senior Project Manager
Christine Kim, PharmD, RAC-US, Senior Project Manager

Office of Combination Products, OCPP, OC
Bindi Nikhar, MD, Associate Clinical Director

SPONSOR ATTENDEES

Name	Job Title/Function
Byoung In Jung	Team Leader, Vice President, Regulatory Affairs Team
Yeosun Hong	Group Leader, Senior Manager, Regulatory Affairs Group
Nayoun Kim	Senior Manager, Regulatory Affairs Group
Sun Ho Ahn	Senior Manager, Regulatory Affairs Group
Shiwon Lee	Manager, Regulatory Affairs Group

Euihan Jung	Group Leader, Director, Regulatory CMC Group
Eunshil Cho	Senior Manager, Regulatory CMC Group
Luke Oh	Group Leader, Vice President, Regulatory Development Group
Kyungho Kim	Director, Regulatory Development Group
Jisuk Ban	Senior Manager, Clinical Development Group
Hyuna Lee	Senior Manager, Clinical Development Group
Youngchun Son	Principal Scientist, Drug Product (DP) Group
Soojeong Park	Principal Scientist, Drug Product (DP) Group
Yeseul Kim	Principal Scientist, Device Group
Jihoon Yoon	Principal Scientist, QC Group
Hana Kim	Senior Manager, Regulatory CMC Group
Garam Lee	Senior Manager, Regulatory CMC Group
Juwon Han	Manager, Regulatory CMC Group
Jeewoong Kim	Scientist, Device Group
Yelena Vaydman	Regulatory Project Manager

1.0 BACKGROUND

SB16 is a human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that is currently being developed as a proposed interchangeable biosimilar to US-licensed Prolia and US-licensed Xgeva. Samsung would like to discuss and obtain feedback on their proposed development plan for SB16.

A Pre-IND BPD Type 2 meeting was held on February 20, 2019, and minutes issued on March 21, 2019. An original IND was submitted on March 29, 2021. Another BPD Type 2 meeting was held on October 21, 2021, for which meeting minutes issued on November 18, 2021.

To support licensure of SB16 (120 mg vial) as a biosimilar to US-licensed Xgeva, Samsung plans to submit the results of the comparative analytical studies of SB16 (60 mg PFS, 120 mg vial), with US-licensed Prolia, EU-approved Prolia, US-licensed Xgeva, and EU-approved Xgeva, as well as the results of the PK similarity and the comparative clinical study with SB16 60 mg PFS without conducting additional clinical studies with SB16 120 mg vial. Samsung plans to seek licensure for all indications previously licensed for US licensed-Prolia and US-licensed Xgeva.

Samsung plans to submit a 351(k) application for SB16 in February 2024 after the successful completion of the planned development program to demonstrate interchangeability between SB16 and US-licensed Prolia and US-licensed Xgeva. The purpose of the current meeting is to discuss the content of the planned BLA submission.

FDA sent Preliminary Comments to Samsung Bioepis Co., Ltd. on September 20, 2023.

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 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

Sponsor's questions are repeated below followed by FDA's response in **bold**, Sponsor's clarifying comments in *italics*, and Meeting discussion in ***bolded italics***. Where applicable, post-meeting comments follow the meeting discussion in **bold**. The Sponsor's clarifying comments, where applicable below, are taken from the Sponsor's slide presentation, which is appended to this document.

Question 1:
Samsung seeks the Agency's agreement and comments on the following points regarding the content of the SB16 BLA:

a. The core eCTD structure.

b. The datasets and dataset standards for the study SB16-1001 and SB16-3001.

c. Given the differences between the two clinical studies SB16-1001 and SB16-3001 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/ISS 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. Based on the FDA Guidance "Bioresearch monitoring technical conformance guide," which advises to include clinical data of all major (i.e., pivotal) studies in bioresearch monitoring (BIMO), Samsung considers that only the data for the Phase III study (SB16-3001) is required to be included in BIMO.

FDA Response to Question 1a:
The proposed core eCTD structure, including placement of the Integrated Summary of Immunogenicity in section 5.3.5.3, is acceptable. In addition to case report forms, please also include narrative summaries for all deaths, serious adverse events and adverse events leading to discontinuation/withdrawal occurring in the comparative pharmacokinetic study and the comparative clinical study in sections 5.3.3.1 and 5.3.5.1, respectively. Note that the study protocols, in addition to the statistical analysis plans, should be included in Module 5.

See additional CMC microbiology comments below.

Sponsor Clarifying Comment for Question 1a:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 1a:
None.

FDA Response to Question 1b:
The approach is acceptable. For the comparative clinical study, please ensure that subject ID numbers are consistent across treatment periods. Also, provide a column showing treatment sequence (e.g., SB16/SB16) so that treatment received following the single transition is clear, and a column indicating during which treatment period (main period or transition period) an event/measurement occurred.

Sponsor Clarifying Comment for Question 1b:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 1b:
None.

FDA Response to Question 1c:
The Division agrees with the proposal for the ISE/ISS.

We have the following additional comments for the clinical study SB16-1001:

- **We note that you applied a sampling duration of 28 weeks for pharmacokinetic analysis in Study SB16-1001. However, we previously recommended a sampling duration of 36 weeks for the PK similarity assessment in the Advice/Information Request letter dated March 14, 2022, since a significant number of subjects may not have a complete PK profile by week 28. You need to justify whether 28-week sampling period is sufficient to capture the complete PK profiles for subjects in Study SB16-1001.**

Sponsor Clarifying Comment for Question 1c:
Refer to slide 7/17 of Sponsor presentation:

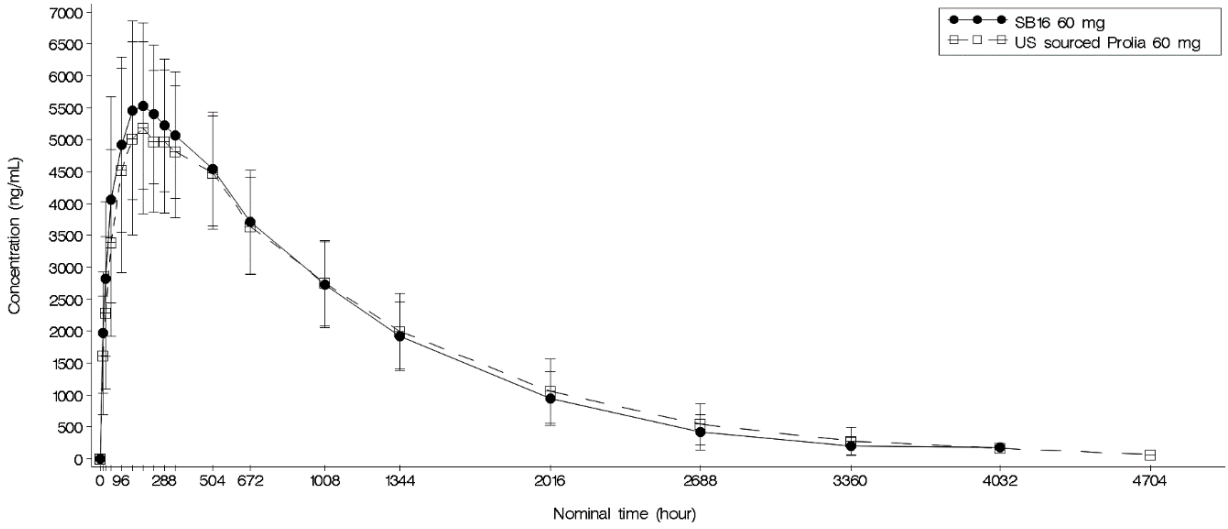
- *Samsung will include justification in the BLA that 28-week sampling period is sufficient to capture the complete PK profiles for subjects in Study SB16-1001.*

- *Details of the justification are provided in the Appendix.*

Refer to slide 15/17 of Sponsor presentation for further explanation:

- *At Day 197 (EOS), all measured serum concentration of denosumab in the PK Analysis Set were below limit of quantification (BLQ), except 7 subjects with near BLQ level (i.e., 20 ng/mL).*

Mean Serum Concentrations vs Nominal Times on Linear Scale of SB16 and USProlia(Pharmacokinetic Analysis Set, Study SB16-1001)



Meeting Discussion for Question 1c:
The Sponsor asked if FDA had any comments regarding their proposed justification. FDA replied that the justification for the 28-week PK sampling duration appears to be acceptable; however, a final decision will be made after reviewing the study data submitted to the BLA.

FDA Response to Question 1d:
Yes. The approach of submitting BIMO data is acceptable.

Sponsor Clarifying Comment for Question 1d:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 1d:
None.

Question 2:
Samsung intends to pursue licensure of SB16 as an interchangeable biosimilar to US Prolia and US Xgeva. Samsung seeks the Agency's agreement and comments on the proposed submission strategy and scope of information to be included with regards to the interchangeability claim of SB16.

FDA Response to Question 2:
We understand that you are planning to seek licensure for SB16 (60 mg/mL single-dose prefilled syringe and 120 mg vial) for the same indications as US-licensed Prolia and US-licensed Xgeva. FDA recommends including your scientific justification for interchangeability to support licensure of SB16 in Module 2.5, Clinical Overview in the BLA submission. The final determination of the adequacy of the data and information submitted to support a demonstration of interchangeability will be made during the review of the application.

We acknowledge the August 2, 2021, submission of use-related risk analysis (URRA) and comparative analyses (CA), however, it was evaluated in the context of biosimilarity. We request that you confirm that there have been no changes to your user interface that would necessitate changes to your URRA and CA in the context of interchangeability since the August 2, 2021, prior submission. Please note, the information can be submitted at the time of the BLA.

Sponsor Clarifying Comment for Question 2:
Refer to slide 8 of Sponsor presentation:

- *Samsung confirms that there have been no changes to the previously Agency-reviewed URRA and CA in the context of interchangeability.*
- *Although minor changes are expected to reflect the updated labelling and risk documents, the changes are not considered to impact the conclusion.*
- *The summary of the changes to URRA and CA will be provided in the BLA submission.*

Meeting Discussion for Question 2:
The Sponsor asked if FDA had further questions or comments. FDA requested that the Sponsor provide detailed information regarding the changes to the URRA and CA, in tabular format rather than a summary. This information should be placed in eCTD Section 5.3.5.4 (other study reports and related information). The Sponsor agreed to provide this information in the BLA submission.

Question 3:
As all safety data for SB16 clinical studies will be provided at the time of the initial BLA submission, there will be no new or additional safety information available at the time of 120-day safety update. Therefore, Samsung intends to submit a waiver accompanied by justification for not providing new safety information in the 120-day safety update, unless Samsung identifies any new safety information. Samsung seeks the Agency's agreement and comments on the proposed approach.

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

Sponsor Clarifying Comment for Question 3:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 3:
None.

Question 4:
According to FDA Guidance "REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry", applicants are required to submit a proposed REMS if the Agency determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. Samsung seeks the Agency's agreement and comments on the following points regarding the development of SB16 REMS in support of a BLA:

a. According to the released REMS list and approved REMS list in the FDA REMS public dashboard, Samsung acknowledges that a REMS was approved for Prolia but not for Xgeva. Based the availability of REMS only for Prolia, Samsung plans to establish a REMS only for SB16 60 mg PFS based on Prolia REMS, and considers that a REMS for SB16 120 mg vial will not be required.

b. Based on section 505-1(i)(1)(B) of the FD&C Act and FDA Guidance "Development of a Shared System REMS Guidance for Industry", the development of a shared REMS for BLAs submitted under section 351(k) of the PHS Act is advised but is under the applicant's discretion. Therefore, Samsung proposes to develop a separate REMS for SB16 60 mg PFS that is comparable to that for Prolia.

c. As Prolia has already completed the requirement of REMS assessment report submission, and safety information of Prolia have been evaluated through accumulated REMS assessment reports of Prolia, Samsung considers the REMS assessment report submission requirement is also not applicable to SB16.

FDA Response to Question 4a:
Yes, we agree with your interpretation that a REMS for SB16 60 mg PFS that is comparable to that for US-licensed Prolia is necessary. At this time, as US-licensed Xgeva is currently approved without a REMS, we anticipate a REMS for SB 16 120 mg vial will not be necessary.

The BLA submission for SB16 60 mg PFS REMS should consist of MS-Word and PDF versions of the REMS Document, REMS Supporting Document, and appended REMS materials (including REMS website screenshots).

Sponsor Clarifying Comment for Question 4a:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 4a:
None.

FDA Response to Question 4b:
Your proposal to establish a separate, comparable REMS to US-licensed Prolia for SB16 60 mg PFS is acceptable. We recognize that it may be in the interest of public health to have a shared system REMS as it may increase efficiencies for multiple parties and stakeholders, but there is no statutory requirement for 351(k) BLA holders to form a shared system REMS.

Sponsor Clarifying Comment for Question 4b:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 4b:
None.

FDA Response to Question 4c:
We do not agree with your assertion that the requirement for REMS assessment report submission is not applicable to SB 16 60 mg PFS.

Pursuant to section 505-1(d) of the Food, Drug, and Cosmetic Act, the REMS must include a timetable for submission of assessments for the SB16 60 mg PFS REMS. The timetable for submission of assessments of the REMS must include an assessment that is 18-months and 3 years after the REMS is initially approved, and within the seventh year after the REMS is approved, or at another frequency specified in the REMS. The REMS Assessment Plan and assessments should consist of metrics, data sources, and methodologies considered relevant for this program to ensure that the REMS is functioning as it is intended and to evaluate whether the goals of the REMS are being met. Refer to the draft guidance for industry *REMS Assessment: Planning and Reporting*.[1]

Sponsor Clarifying Comment for Question 4c:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 4c:
None.

[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.

Question 5:
Samsung seeks the Agency's agreement and comments on the preliminary manufacturing schedule of the SB16 DS and DP (60 mg PFS and 120 mg vial), which is within (b) (4) months after submission of the BLA, in support of the pre-license inspection (PLI).

FDA Response to Question 5:
The proposed manufacturing schedule of the SB16 DS and DP (60 mg PFS and 120 mg vial) to be within (b) (4) months after submission of the BLA appears to be acceptable. If possible, please schedule the manufacturing of SB16 DS and SB16 120 mg vial DP at Samsung Biologics Co., Ltd. to be close to each other, so that both can be covered during the same pre-license inspection.

Sponsor Clarifying Comment for Question 5:
None; Sponsor accepts FDA response.

Meeting Discussion for Question 5:
None.

Question 6:
For the SB16 BLA, Samsung plans to claim the shelf-life of SB16 DS, 60 mg PFS DP, and 120 mg vial DP and submit supportive stability data as follows:

a. Samsung intends to claim the shelf-life of SB16 DS as (b) (4), based on 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 SB16 60 mg PFS DP as 36 months, based on real-time long-term stability data of three clinical phase batches available during the BLA review cycle.

c. Samsung intends to claim the shelf-life of SB16 vial DP (120 mg) as 36 months, based on real-time long-term stability data of three clinical phase batches available during the BLA review cycle.

Does the Agency agree or have any comments?

FDA Response to Question 6:
Insufficient information is provided in the meeting package to make a determination on the acceptability of the selected batches for shelf-life determination. Leveraging of stability data from engineering run (ER) and clinical batches to support the shelf-life determination of commercial batches may be acceptable, provided that the manufacturing processes and storage conditions for the ER/clinical batches are representative of the commercial process. Ultimately, the adequacy of the data to support the comparability of clinical phase

and PPQ/commercial materials as well as the types and extent of data needed to support the DS/DP shelf-life is a review issue. To that end, provide sufficient data to support a reasonable shelf-life for SB16 drug product (DP) to allow for distribution. While it may be acceptable to provide a stability update after the initial BLA submission, per BsUFA III, these data should be submitted within 30 days of the original application. In addition, we have the following comments:

a) **From the information provided in Table 2-1 you intend to make available up to (b) (4) of long-term stability data for three drug substance (DS) batches (1 ER and 2 clinical) by (b) (4) from the initial BLA submission in support of a (b) (4) DS shelf-life. We do not agree with your proposed timeline for this delayed data submission since this does not allow adequate time for review.**

b) **Table 2-2 indicates that up to 36 months of long-term stability data will be provided at the initial BLA submission for three clinical phase PFS DP batches to support the shelf-life. This appears reasonable to support a 36-month shelf-life.**

c) **Table 2-4 indicates that a maximum of 24 months of stability data will be provided for three clinical phase DP batches to support a shelf-life of 36 months for DP packaged in a vial. This is not sufficient to support a 36-month shelf-life. We recommend that you include protocols in Sections 3.2.S.7.2 and 3.2.P.8.2 for expiry extension of DS and DP as new stability data become available.**

Sponsor Clarifying Comment for Question 6a and 6c:

Refer to slide 9 of Sponsor presentation:

- *Samsung proposes to provide long-term stability data of (b) (4) DS clinical batches and 36- month vial DP clinical batches by Month 4 (Jun 2024) from the submission of the initial BLA, in support of a (b) (4) DS shelf-life and 36-month vial DP shelf-life.*
- *Nonetheless, Samsung would like to seek the Agency's advice on by when the updated stability data can be submitted for consideration into the shelf-life claim, allowing time for the Agency's review.*

Meeting Discussion for Question 6:

The Sponsor asked if FDA has comments on their proposed approach. FDA pointed out that the Agency's approach has been consistent among the denosumab biosimilar products. FDA also emphasized that although BSUFA III Performance Goals and Procedures specifies that delayed data submission is acceptable, it should be submitted within 30 days of the original application submission and recommended that the sponsor commits to this; however, in this particular situation it may be acceptable to submit data within 4 months of the initial BLA submission. Regarding leveraging stability data from the engineering

run and clinical batches to support the shelf-life determination of commercial batches, this may be acceptable provided manufacturing processes and other conditions of the clinical batches are representative of the commercial product and process; this will be a review issue. The Sponsor committed to providing the stability data updates by month 4 of the initial BLA submission. Regarding the representativeness of the clinical and engineering run batches for the commercial batches, they will submit the respective data on the comparability in the BLA.

Question 7:

(b) (4) (b) (4) Samsung seeks the Agency's agreement and comments on the proposed approach.

FDA Response to Question 7:
Regarding the SB16 PFS presentation, (b) (4) (b) (4) (b) (4) **The final evaluation of the adequacy of the** (b) (4) **approach and data will be conducted during the BLA review.**

Sponsor Clarifying Comment for Question 7:
Refer to slide 11 of Sponsor presentation:

- (b) (4)
-

Meeting Discussion for Question 7:
The Sponsor asked if FDA had further questions or comments, and FDA said that the Sponsor's proposal appears acceptable.

Question 8:
To support packaging process validation of SB16 PFS, (b) (4) (b) (4) (b) (4)

[redacted] Samsung seeks the Agency's advice and comments on the proposed approach.

FDA Response to Question 8:
From a product quality perspective, we do not agree with your proposed approach [redacted] To support licensure, submission of PPQ batch results for SB16 are needed. We recommend including packaging validation data for the process validation batches of SB16 at the time of the BLA submission. In addition, an assessment of the impact of the packaging process on product (SB16) quality was not provided in the meeting package. We strongly recommend using the product itself to assess the impact of this manufacturing step on both device and product quality.

The process validation data provided should include container closure integrity test results obtained after the PFS assembly process of SB16 [redacted]. In addition, you indicate in the meeting package that no process parameter is established for [redacted]. Provide in the BLA a justification for how it is ensured that [redacted].

Sponsor Clarifying Comment for Question 8:
Refer to slide 12 of Sponsor presentation:

- *In accordance with the Agency's comments, Samsung will submit PFS packaging process validation data performed for SB16, including the requested data in the preliminary comments, or justification in case not provided.*

Meeting Discussion for Question 8:
The Sponsor asked if FDA had further questions or comments. FDA said that the Sponsor's response is acceptable but noted that it is not clear if they are responding that they could provide justification in both cases. The Sponsor stated that they will submit PFS packaging process validation data for SB16 to assess the impact of product quality and to assess the CCIT. Regarding the justification for [redacted], the Sponsor clarified that the requested data that were outlined here will be provided either as a justification or the actual data will be provided in the BLA; the justification is only about the [redacted] process. FDA said that this is acceptable.

Question 9:
Samsung seeks the Agency's agreement on the delayed submission data package to be filed 30 days after the initial BLA submission for SB16.

FDA Response to Question 9:
As stated in the response to Question 6, while it may be acceptable to provide a stability update after the initial BLA submission, consistent with BsUFA III, Performance Goals and Procedures, these data should be submitted no later than 30 calendar days after the submission of the original application. We do not agree with your plan to extend the shelf life by submitting stability data (b) (4) from the initial submission.

Sponsor Clarifying Comment for Question 9:
Refer to slide 10 of Sponsor presentation:

- *As proposed in Q6a and Q6c, Samsung proposes to provide stability updates by Month 4 (June 2024) from the initial BLA submission in support of the shelf-life of SB16.*
- *Accelerated stability data of 6-month PPQ PFS DP will be provided by June 2024.*
- *Long-term functional stability data of 6-month assembled PFS FDP device will be provided by June 2024.*
- *Accelerated functional stability data of 6-month assembled PFS FDP device will be provided by June 2024.*
- *Accelerated functional stability data of 9-month assembled PFS FDP device will be provided by August 2024, as supportive data of the shelf-life claim of PFS (36 months).*

Meeting Discussion for Question 9:
The Sponsor asked if FDA had any comments on their proposal. FDA said that, like with their response to Question 6, for this particular situation it may be acceptable to submit stability updates within 4 months of the initial BLA submission and reiterated their preference to abide by BSUFA III guidelines regarding submission of data beyond 30 days of the initial submission. FDA asked the Sponsor to clarify if they were talking about the prefilled syringe (PFS) data to be submitted by August 2024. The Sponsor clarified that they plan on submitting by month 4 functional stability data of the final drug product as supportive of the shelf-life claim. The shelf-life claim will be mostly based on the stability data from clinical batches for the PFS. Complete data will be provided by month 4 to support the proposed shelf-life claim of 36 months. The functional stability data provided by August 2024 is supportive data for the shelf-life claim of the PFS. FDA pointed out that the shelf-life is a review issue; for combination products there is input from both a drug and a device perspective. Whichever is the shorter of those two will be the shelf-life. FDA recommended including tables in the Sponsor's application describing any differences between the stability lots and the proposed commercial product. If the Sponsor is using clinical batches to

support the shelf-life of the commercial product then the Sponsor should comment on how the clinical batches compare to what the Sponsor proposes for commercial product from a drug and a device perspective. The Sponsor agreed to include the requested information in the BLA. FDA said that they would ensure that all review team members are in agreement and may provide a post-meeting comment if needed.

Post-Meeting Comment for Question 9:
FDA confirms that all review team members are in agreement with the approach outlined in our response above.

Additional New Question from Sponsor:
Refer to slides 13-14 of Sponsor presentation:
During the GCP inspection (Request #16) of Samsung's another product, SB12 (proposed eculizumab biosimilar, BLA# 761340), Samsung was questioned whether the clinical sites were waived for signed Form 1572 requirements, while the clinical study was conducted only outside the US.

With respect to SB16, Samsung has conducted Phase I clinical study (SB16-1001) as a multinational study at two clinical sites in US and one clinical site in France. The sites in the US are included under IND, and the one in France is not included under IND, while the study was conducted under the same protocol for all sites. For the investigators from the French site, Samsung collected complete, signed GCP statements to ensured to conduct the clinical study in accordance with ICH E6 (R2).

According to FDA guidance "Frequently Asked Questions Statement of Investigator (Form FDA 1572)", the investigators from the foreign sites that are not included under the IND are not required to sign the 1572. And, if the study data from a non-IND site is to be submitted to support a marketing application, the study at the non-IND site should be compliant to 21 CFR 312.120 (GCP compliance for foreign clinical sites not conducted under IND).

Since all GCP statements compliant to ICH E6 (R2) are collected from investigators in French site of SB16 Phase I clinical study, Samsung considers that it is not necessary to submit, nor to request a waiver for, signed FDA Form 1572 from investigators in French site.

Does the Agency have any comments on this approach?

Meeting Discussion for Additional New Question:
The Sponsor clarified that there was one "phase 1" clinical study that was conducted at three sites; two sites were in the US and one site was in France. The two sites in the US are registered under the IND; the remaining site in France is not registered under the IND. FDA said that while this is not the usual approach taken, it is permissible to have a non-IND foreign clinical site as part of an overall

multi-national study conducted under an IND. FDA also reminded the Sponsor to note in 21 CFR 312.120(b) that there is a detailed outline of the supporting information that must be included in your marketing application if you intend to include data from the foreign clinical site that was not included in the IND in support of your marketing application. The Sponsor stated that they will make note and check that section to be sure that the necessary data that are included in the BLA. FDA commented that from a clinical perspective sponsors generally submit waiver requests when the study is being submitted and conducted under the IND, not at the end, so this is a somewhat unusual situation. The Sponsor stated that according to the guidance, investigators from non-IND foreign sites are not required to sign the form 1572, and wanted to be sure this understanding is aligned with FDA. FDA acknowledged this and noted that typically the study sites are specified in the protocol up-front. The Sponsor will review the CFR citation to ensure that all necessary requirements are fulfilled.

Additional Comments:

Combination Products:

1. **The proposed SB16 prefilled syringe is a single-entity biologic-device combination product per 21 CFR Part 3.2(e)(1). Combination products are subject to 21 CFR Part 4.A "Current Good Manufacturing Practice Requirements for Combination Products".[2] 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). For additional information see the related guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*.**

2. **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.**

3. **For location of information on the device constituent part see the FDA eCTD Technical Conformance Guide: Technical Specifications Document, available by reference in the guidance for industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.**

[2] Refer to FDA's website for more details: https://www.federalregister.gov/documents/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

4. **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, refer to FDA's website.[3]**

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.

5. **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.**

6. **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**

[3] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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).

7. 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*.

a. 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 (differential pressure when a peristaltic pump is used), 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 syringes.

iv. Parameters for filling and capping for the vials.

v. 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.

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

vii. **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.**

b. **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.**

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

c. 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 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.

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

iv. 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.

3.0 OTHER INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion regarding the approach to developing the content for a REMS and patient labeling (e.g., Medication Guide) was held. Refer to the discussion under Question 4.

- 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[4]. 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)[5] and 201.57[6] 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*[7] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[8]

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.[9]

- 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

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[5] 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
[6] 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
[7] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[8] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[9] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

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*.[10]

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.

[10] 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[11] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[12]. 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:

[11] https://www.fda.gov/media/84223/download
[12] 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[13] 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.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

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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.

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