

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761059Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



BLA 761059

REFUSAL TO FILE

Samsung Bioepis Co., Ltd.
c/o Biologics Consulting Group, Inc.
400 N. Washington Street, Suite 100
Alexandria, VA 22314

Attention: Yelena Vaydman
US Agent Project Manager

Dear Ms. Vaydman:

Please refer to your Biologics License Application (BLA), dated August 29, 2016, received August 29, 2016, submitted under section 351(k) of the Public Health Service Act for SB5, a proposed biosimilar to Humira.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 601.2(a) for the following reasons:

Your 351(k) Biologics License Application (BLA) 761059 did not include a drug ^{(b) (4)} [REDACTED], the DS manufacturing site listed in your FDA FORM 356h. We requested a manufacturing schedule in an information request, dated October 17, 2016. In your response, dated October 20, 2016, you stated that “there is no production scheduled for SB5 drug substance manufacturing at ^{(b) (4)} [REDACTED].” Title 21 of the Code of Federal Regulations section 600.21 states that “The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired.” According to Title 21 of the Code of Federal Regulations section 601.20(b), no biologics license shall be issued unless “such product is available for inspection during all phases of manufacture.” Because SB5 will not be available for inspection at the ^{(b) (4)} [REDACTED] site listed in the FDA FORM 356h of your 351(k) BLA, your application is not complete. Therefore, we are refusing to file your 351(k) BLA under 21 CFR 600.21 and 601.20(b).

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a BPD Type 1 Meeting about our refusal to file the application. A meeting package should be submitted with this BDP Type 1 meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

If you have any questions, call Brandi Wheeler, Regulatory Project Manager, at (301) 796-4495.

Sincerely yours,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
10/28/2016



PIND 118299

MEETING MINUTES

Samsung Bioepsis Co., Ltd.
c/o Biologics Consulting Group, Inc.
400 N. Washington Street
Suite 100
Alexandria, VA 22314

Attention: Yelena Vaydman

Dear Ms. Vaydman:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SB5.

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2016. The purpose of the meeting was to discuss the format and content of biosimilar biological product application for SB5.

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

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: Biosimilar Biological Product Development (BPD) Type 4
Meeting Date and Time: May 4, 2016 at 1:00 pm – 2:30 pm
Meeting Location: FDA White Oak, Bldg 22, Rm 1311
Application Number: PIND 118299
Product Name: SB5 (proposed biosimilar to US-licensed Humira)
Indication: SB5 is being developed for the same indications as approved for US-licensed Humira
Sponsor Name: Samsung Bioepis Co.
c/o Biologics Consulting Group, Inc.
Meeting Chair: Sarah Yim, MD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Sarah Yim, MD, Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Janet Maynard, MD, Clinical Team Leader, DPARP
Suzette, Peng, MD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader, DPARP
Andrew Goodwin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Howard Anderson, PhD, Team Leader Product Quality, Division of Biotechnology Review and Research III
Richard Ledwidge, PhD, Biologist, Division of Biotechnology Review and Research III
Anshu Marathe, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II
Lei He, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II
Greg Levin, PhD, Lead Mathematical Statistician, Division of Biometrics II
Yongman Kim, PhD, Mathematical Statistician, Division of Biometrics II
Yi Tsong, PhD, Supervisory Mathematical Statistician, Division of Biometrics VI
Xiaoyu (Cassie) Dong, PhD, Mathematical Statistician, Division of Biometrics VI
Jessica Lee, PharmD, Regulatory Project Manager, DPARP
Sue Lim, M.D., Medical Officer, Therapeutic Biologics and Biosimilars Staff (TBBS)
Stacey Ricci, ScD, Senior Toxicologist, TBBS
Daniel Orr, J.D., Regulatory Counsel, Division of Regulatory Policy I

Tyree Newman, Project Manager, TBBS
Jessica J. Lee, MD, Clinical Team Leader, Division of Gastroenterology and Inborn Errors
Carlos Mena-Grillasca, Rph, Safety Evaluator, DMEPA, OSE
Robert Meyer, BSME, Mechanical Engineer, CDRH

SPONSOR ATTENDEES

Hee Kyung Kim, Senior Vice President, Regulatory Affairs Team
Young Phil Lee, Vice President, Quality Evaluation Team
Inyoung Baek, Director, Medical & Lifecycle Safety Team
Jeehoon Ghil, Director, Medical & Lifecycle Safety Team
Hyung Ki Park, Director, Regulatory Affairs Team
Byoung In Jung, Senior Manager, Regulatory Affairs Team
Sung Eun (Jessica) Bae, Associate, Regulatory Affairs Team

From [REDACTED] ^{(b) (4)} *Sponsor's US Agent* [REDACTED] ^{(b) (4)}

Joining by phone from Korea

Yong Kook Kim, Vice President, Drug Product Team
Won Young Yoo, Director, Cell Line Development Group, Cell Engineering Team
Jae Sun Lee, Principal Scientist, Cell Culture Process Group, Drug Substance Team
Yoon Seok Lee, Director, Purification Process Group, Drug Substance Team
Jae Il Lee, Director, Analytical Method Development Group, Quality Evaluation Team
Yeon Joo Hong, Principal Scientist, Bioassay Group 1, Quality Evaluation Team
Jung Won Kang, Principal Scientist, Bioassay Group 1, Quality Evaluation Team
Kyung Eun Kim, Principal Scientist, Bioassay Group 1, Quality Evaluation Team
Sera Kim, Senior Scientist, Analytical Method Development Group, Quality Evaluation Team
Sang Il Lee, Principal Scientist, Process Innovation Team
Tae Heui Lee, Senior Manager, Program Management Team
Hyoung Taek Lim, Senior Manager, Manufacturing Management Group
Donghoon Shin, Director, Medical & Lifecycle Safety Team
Soo Yeon Cheong, Senior Manager, Medical & Lifecycle Safety Team
Youmee Choi, Senior Manager, Intellectual Property Team
Kyungho Kim, Senior Manager, Regulatory Affairs Team
Saeromi Kim, Manager, Regulatory Affairs Team
Haesoo Kim, Manager, Regulatory Affairs Team
Mun Jung Kim, Manager, Regulatory Affairs Team

1.0 BACKGROUND

In a submission dated, February 26, 2016, Samsung requested a Biosimilar Biological Product Development (BPD) Type 4 meeting to discuss the format and content of biosimilar biological product application for SB5. The meeting was granted on March 9, 2016. The sponsor's questions from the Briefing Package dated, February 26, 2016, are listed below in *italics* and the

FDA responses and meeting discussions are provided in normal font.

Prior to the May 4, 2016, Samsung provided slides to review and discuss at the meeting. The slides are attached in Section **6.0 ATTACHMENTS AND HANDOUTS** 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 Samsung Bioepis Co., LTD. and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

FDA sent Preliminary Comments to Samsung on May 2, 2016

2. DISCUSSION

Question 1:

The Applicant established release and shelf-life specifications for SB5 DS and DP based on the product risk assessment. Does the Agency agree that the proposed release and stability specifications for SB5 DS and DP are adequate and sufficient for the 351(k) application?

FDA Response to Question 1:

No, we do not agree. While an overall control strategy was not provided in the submission, the proposed SB5 DS and DP release and stability testing strategy does not appear to adequately control for purity, biological activity, and pharmacokinetics. Therefore, we have the following recommendations:

- a. Add a CE-SDS assay under reducing conditions for drug substance and drug product release and stability testing to provide additional control for purity.
- b. Add Oligosaccharide content, Fc receptor binding, and Fc complement binding assays for drug substance release testing to provide additional control for biological activity and pharmacokinetics.
- c. Describe the control strategy for process related impurities such as host cell proteins, and host cell DNA in the BLA submission. Alternatives to the proposed recommendations may be acceptable if purity, biological activity, and attributes that impact pharmacokinetics are sufficiently controlled in the overall SB5 control strategy.

Discussion to Question 1:

The Sponsor provided further information in slides 7-13 regarding the quality development of SB5 and their proposed control strategy. The FDA did not provide specific comments to the information presented by Samsung at the meeting on May 4, 2016, but confirmed this was the type of data that should be submitted to demonstrate control and informed the Sponsor to provide

the data in the BLA application. Furthermore, the adequacy of the data will be determined during the BLA review.

Question 2:

The Applicant proposes to claim expiry dating of SB5 drug substance (DS) as (b) (4) months based on (b) (4) months long-term stability data of PVR DS batches expected to be available at the time of licensure plus additional 6 months based on the comparability between the clinical and PVR batches. Does the Agency have any other comments?

FDA Response to Question 2:

The FDA may allow additional extension of the expiry at licensure beyond the PVR real time stability results. However, the establishment of a dating period is determined during review as it is based on a demonstration of comparability between clinical and PVR lots and the stability results provided.

Discussion to Question 2:

No discussion.

Question 3:

The Applicant proposes to claim expiry dating of SB5 drug product (DP) as (b) (4) months based on (b) (4) months long-term stability data of PVR DP batches expected to be available at the time of licensure plus additional 6 months based on the comparability between the clinical and the PVR batches. Does the Agency have any other comments?

FDA Response to Question 3:

Please see our response to question 2. However, as per ICHQ5C, a minimum of 6 months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested on at least 3 batches produced at commercial scale in the final container closure system.

Discussion to Question 3:

Samsung requested clarification if the shelf life claim can be based on 3 clinical batches at the time of licensure as Samsung states their clinical batch is representative of PVR/commercial batch (refer to slide 15). The sponsor was informed that the shelf life determination is made during the BLA review and is based on real time stability results as per ICHQ5C. The dating period will be based on real time data from commercial process lots however clinical lots can be used to support or possibly extend the dating period beyond the real time PVR results depending on how representative the clinical process is to the commercial process and a demonstration of comparability between the clinical and commercial products.

Question 4:

The Applicant has performed comparability assessment to demonstrate the comparability between SB5 pilot, clinical, and PVR batches in terms of structural, physicochemical, biophysical, and biological characteristics. Does the Agency have any further comments whether the Applicant's comparability assessment strategy is adequate and sufficient to be included in 351(k) application for the Agency's review?

FDA Response to Question 4:

The determination of comparability between the clinical and PVR material and the suitability of the comparability range acceptance criteria for the comparability exercise are a review issue; however, your proposed approaches to establishing comparability appear reasonable. Provide degradation slope plots for critical quality attributes for the accelerated/stress studies. The degradation slopes are needed to evaluate the rate of product breakdown. The breakdown rate is often a sensitive indicator of changes in quality attributes following process changes and should be carefully evaluated in the comparability study. In addition, provide representative primary data such as chromatographs, gels, dose response curves, etc. in the BLA submission to facilitate an independent evaluation of the comparability results.

Discussion to Question 4:

No discussion.

Question 5:

The Applicant has performed extensive quality similarity studies to demonstrate similarity between SB5 and Humira® in terms of structural characteristics (primary, higher-order, and glycosylation), physicochemical properties (charge heterogeneity, purity, and impurity), and biological activities (Fab-related functions and Fc-related functions). The Applicant believes that the proposed strategy of quality similarity assessments, in terms of criticality risk assessment-based tiered system, is sufficient to demonstrate similarity in quality between SB5 and Humira® in support of a 351(k) application. The Applicant's approach was also presented in Question 1 of the BPD Type 2 meeting request made in December 18, 2015, with the updates that have been made to reflect the Agency's recommendations given during the Type 4 BPD meeting for another proposed biosimilar product by the Applicant (i.e. SB2; the Type 4 BPD meeting for SB2 was held on December 14, 2015). Does the Agency have any further comments?

FDA Response to Question 5:

We have the following comments regarding your proposed analytical similarity assessment:

First, we have concerns regarding the limited number of SB5 lots used for the equivalence test in Tier 1. Specifically, considering the potential high variability of two tier 1 quality attributes (potency: TNF- α neutralization by TNF- κ 0B reporter gene; TNF- α binding assay), six drug product lots of SB5 may not be sufficient to estimate the data variability. Thus, we highly

recommend that you increase the number of lots for SB5 drug product. In addition, clarify the number of drug product (DP) lots you plan to use in Tier 2 and Tier 3 assessment. We note that the 1st DP lot manufactured from each drug substance batch will be included in Tier 1 equivalence testing. However, it is not clear if you plan to use all the available DP lots (9 lots) or only the independent DP lots (6 lots) for Tier 2 and Tier 3.

Second, if EU-approved Humira is the sole comparator in your comparative clinical studies, you should establish a scientific bridge between US-licensed Humira and EU-approved Humira. That is, three pair-wise comparisons (between SB5 and US-licensed Humira, SB5 and EU-approved Humira, and US-licensed Humira and EU-approved Humira) should be included in your analytical similarity assessment. Note, we addressed this issue in the Advice Letter dated March 18, 2016.

Third, with 6 independent DP lots and more than 30 reference lots, you can use all the reference lots to compute the reference variability and mean values and use up to 10 reference batches for the sample size in the confidence interval calculation for Tier 1 equivalence test. With 6 DP lots from SB5 and 10 US-licensed Humira lots, we recommend a confidence level of 87% for the confidence interval.

Discussion to Question 5:

Regarding Tier 1 equivalence testing (slide 17), Samsung presented a revised strategy whereby they will increase the number of DP lots for Tier 1 equivalence testing from 6 lots to 9 lots because they interpreted FDA's response to Question 5 to mean that DP manufactured using the same DS can be considered independent. FDA corrected this misunderstanding, and clarified that multiple DP lots manufactured from the same DS lot are not considered to be independent DP lots. FDA advised that Samsung's revised strategy may not change the variability of the Tier 1 quality attributes because most attribute variability, is derived from individually manufactured DS lots, and not DP lots manufactured from the same DS lot. Therefore, increasing the number of DP lots derived from the same DS lots is not expected to impact variability for certain attributes.

FDA agreed with Samsung's proposal to use all available SB5 DP lots (9 lots) for Tier 2 assessments and to use between 2 and 9 SB5 DP lots for Tier 3 assessments, where the number of lots used would depend on the Tier 3 quality attribute being assessed.

The Sponsor requested clarification for the reasoning used in FDA's approach in adjusting the confidence level and the number of reference batches for deriving the confidence interval. FDA advised the Sponsor that the confidence interval of 87% was derived from 6 biosimilar lots and 10 reference lots.

Post-meeting comment:

Regarding the determination of the confidence level for the Tier 1 equivalence test, FDA recommends using a 90% confidence level if a sponsor has 10 biosimilar lots and 10 reference product lots. Considering the limited number of independent SB5 DP lots you currently propose

to include in Tier 1 testing, FDA recommends that Samsung include additional DS lots in Tier 1 testing in order to have more reliable estimates for SB5 variability. However, the DP lot selection plan from unique DS lots should be pre-specified.

Question 6:

SB5 has been developed in a Safety pre-filled syringe (PFS) presentation which consists of primary packaging (syringe with needle, rigid needle shield, and plunger rubber) and secondary packaging (safe-shield body, plunger rod, and finger flange). In addition, SB5 has been developed in an autoinjector (AI) presentation which consists of PFS and two separate subassemblies (front subassembly and rear subassembly) which when assembled, covers the PFS to form the AI.

As SB5 drug product (DP) formulation does not come into contact with any of the secondary packaging components, the stability studies on DP have been conducted in the primary packaging of Safety PFS without any secondary packaging components. In addition, as the primary packaging of the AI is same as that of Safety PFS, no additional stability studies on DP for AI presentation has been performed. This approach was discussed and agreed on by the FDA in a written response to the BPD Type 2 meeting request (January 29, 2015). Does the Agency have any further comments?

FDA Response to Question 6:

The approach described in the written response to the BPD Type 2 meeting request (January 29, 2015) is acceptable. There are no additional comments.

Discussion to Question 6:

No discussion.

Question 7:

The Applicant plans to submit a 351(k) application containing a full data set from Phase I study in healthy subjects and from 52-week Phase III study which includes a randomized, double-blind period of 24 weeks and a transition-extension period of 28 weeks. Pharmacokinetics (Phase I study in healthy subjects and supportive PK assessment in Phase III study in RA patients) and efficacy and safety (Phase III study) profiles were shown to be similar between SB5 and Humira®. In addition, there were no safety, immunogenicity, or diminished efficacy issues after transition from Humira® to SB5. The Applicant believes that these study results present sufficient clinical evidence for similarity between SB5 and Humira® for the BLA submission. Does the Agency agree?

FDA Response to Question 7:

The proposed clinical data to support the 351(k) application seems reasonable. Whether the study results present sufficient clinical evidence to support a determination that there are no clinically meaningful differences between SB5 and the reference product will be a review issue.

Additional Statistical Comments:

- a. Your primary analysis for Study SB5-G31-RA was carried out in a per-protocol population using a 95% confidence interval and a similarity margin of $\pm 15\%$. We currently recommend that the primary analysis be carried out in all randomized patients and we expect the overall type I error rate to be controlled at 5%, i.e., a 90% confidence interval for the difference in ACR20 responses can be compared to the margin. Furthermore, we recommend a similarity margin with a lower bound no greater in magnitude than -12% . You should justify in your application that the primary results meet these criteria.
- b. Clarify whether you continued collecting safety and efficacy data through the final time point of all key comparisons, even in patients who discontinued the study treatment, to help prevent missing data in intention-to-treat analyses in the comparative clinical study. If such data are available, you should carry out supportive intention-to-treat analyses that include all data regardless of treatment adherence.
- c. It appears that approximately 7% of patients dropped out of the study before the Week 24 assessment. We do not agree that the sensitivity analyses discussed in the meeting package will sufficiently explore the potential effect that violations of the assumptions about missing data might have on the reliability of results. To further assess the robustness of the primary analysis results with regards to missing data, we recommend that you conduct additional tipping point sensitivity analyses in the full analysis set. These analyses should vary assumptions about outcomes among the subsets of patients on the two treatment arms who withdrew from the study early. These varying assumptions should include the possibility that patients with missing data on the SB5 arm had dissimilar outcomes than dropouts on the EU-approved Humira arm. The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of similarity. The plausibility of those assumptions can be discussed.

Discussion to Question 7:

- a) The Sponsor indicated that they would provide results based on a 90% confidence interval for the difference in ACR20 response at Week 24 and use the recommended 12% lower bound for the margin. The Sponsor inquired about the justification for the 12% margin. FDA indicated that the recommended margin was based on a balance between clinical relevance and feasibility and stated that more details on the rationale for the recommendation would be provided in a post-meeting note (see note at the end of the minutes).

- b) The Sponsor was advised in future studies to continue to follow patients for safety who have discontinued the study treatment to help prevent missing data in important intent-to-treat analyses.
- c) FDA agreed with the Sponsor's proposal to perform a tipping point analysis with varying assumptions about outcomes among the early withdrawn patients to compare the equivalence margin of 12% with a 90% confidence interval for the difference in ACR20 responses at Week 24.

Question 8:

The clinical study program of SB5 consists of four studies. Two clinical studies were conducted in support of a clinical development of SB5 for the PFS presentation- a Phase I study in healthy volunteers (SB5-G11-NHV) and a Phase III study in RA patients (SB5-G31- RA). Two additional clinical studies were conducted in support for the AI presentation- a Phase I comparative PK bridging study in healthy subjects (SB5-G12-NHV) and a Phase II usability study in RA subjects (SB5-G21-RA). The clinical overview (Section 2.5) and the summaries (Summary of Clinical Efficacy in Section 2.7.3 and Summary of Clinical Safety in Section 2.7.4) in Module 2 of the CTD will include the results of these four studies. However, no pooled analyses across these studies will be performed due to the differences between the studies (i.e. study populations, objectives, treatment regimen, etc.). Instead, clinical studies' results will be presented side-by-side without any integrated analyses.

Also, Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) will be based on the Section 2.7.3 and 2.7.4, respectively, without any pooled analyses. Does the Agency agree with this approach?

FDA Response to Question 8:

Given the differences between your 4 clinical studies, we agree that pooled analyses would not be informative. In regards to the ISE and ISS, if you anticipate that section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) will each be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, we agree with your plan to place the summary portion of your integrated assessments in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. We note your proposal to provide an explanation in both Module 2 and Module 5.

Discussion to Question 8:

No discussion.

Question 9:

The Applicant proposes a delayed submission in accordance with guidance to update data for several stability studies submitted with the original application. The data to be updated as part of a delayed submission is as follows: 6 month long-term stability data for PVR DP, 6 month

leachables study data for PVR DP, 6 month functional stability data under real-time aging condition for Safety PFS and AI, and aging equivalent 2 years at RT functional stability data under accelerated condition for Safety PFS and AI. The corresponding CTD sections will be updated accordingly and submitted at the time of the delayed submission.

Does the Agency agree with this approach?

FDA Response to Question 9:

Yes, we agree with the proposed delayed submission approach.

Additional Comment: A safety assessment of extractables and leachables with the pre-filled syringe (and auto-injector as appropriate) should be available with the BLA and/or as part of a delayed submission.

Discussion to Question 9:

Please refer to slide 26 in Section **6.0 ATTACHMENTS AND HANDOUTS**.

Additionally, FDA found it acceptable that the Sponsor provides the safety pre-filled syringe (PFS) final assembly process validation as part of a delayed submission.

Question 10:

Assuming similarity between SB5 and US Humira® has been demonstrated through extensive quality similarity exercises, a series of non-clinical studies, a Phase I study in healthy subjects, and a Phase III study in RA subjects, there is no reason to expect any difference in efficacy and safety between SB5 and Humira® in other patient populations for which Humira® is indicated. Does the Agency agree that similarity between SB5 and US Humira® has been demonstrated and that the efficacy and safety observed in the selected reference indication, RA, can be extrapolated to all other adult therapeutic indications currently authorized for Humira®?

FDA Response to Question 10:

As already noted, whether the data you intend to submit supports a determination that SB5 is biosimilar to US-licensed Humira will be a review issue. If SB5 meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, you may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed. However, you would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought. Such scientific justification for extrapolation should address, for example, the following issues for the testing and extrapolating conditions of use:

- a. The mechanism(s) of action in each condition of use which licensure is sought; this may include:
 - I. The target/receptor(s) for each relevant activity/function of the product;
 - II. The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
 - III. The relationships between product structure and target/receptor interactions;
 - IV. The location and expression of the target/receptor(s).
- b. The pharmacokinetics and biodistribution of the product in different patient populations; relevant PD measures also may provide important information on the mechanism of action.
- c. The immunogenicity of the product in different patient populations.
- d. Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities).
- e. Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought

The validity of your scientific justification based on the mechanism(s) of action of adalimumab and these additional factors listed above for extrapolating clinical data to indications other than rheumatoid arthritis will be a review issue.

The reference product has orphan drug exclusivity for some indications, which would preclude approval of a biosimilar to US-licensed Humira for the protected indication until the expiration of orphan drug exclusivity. These indications include hidradenitis suppurativa.

You can submit data and information intended to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for an indication for which the reference product has unexpired orphan exclusivity. However, the Agency will not be able to approve SB5 for the protected indication(s) until the orphan exclusivity expires.

We note that your question is only related to adult indications. You will need to address the Pediatric Research Equity Act (PREA) for all indications previously approved for the reference product for which you seek licensure. See our response to Question 11 below.

Discussion to Question 10:

Please refer to slides 27 and 28 in Section **6.0 ATTACHMENTS AND HANDOUTS**.

Post-Meeting Comment:

Please refer to the FDA communication to Samsung, “Post Meeting Comments for iPSP,” dated May 17, 2016, an excerpt of which is provided below. FDA would like to clarify that a portion of the original response provided for Question 10 was in error (erroneous text shown in strikethrough below). This also clarifies what was conveyed by the Agency during the meeting itself.

~~“The reference product has orphan drug exclusivity for some indications, which would preclude approval of a biosimilar to US-licensed Humira for the protected indication until the expiration of orphan drug exclusivity. These indications include hidradenitis suppurativa.~~

~~You can submit data and information intended to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for an indication for which the reference product has unexpired orphan exclusivity. However, the Agency will not be able to approve SB5 for the protected indication(s) until the orphan exclusivity expires.”~~

For certain indications, such as JIA in 2-4 year-olds and pediatric Crohn’s disease in 6-17 years, you can submit data and information intended to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for an indication for which the reference product has unexpired orphan exclusivity. However, the Agency will not be able to approve SB5 for the protected indication(s) until the orphan exclusivity expires.

Question 11:

Since SB5 is developed as a biosimilar of Humira®, and the similarity has been demonstrated from the quality, non-clinical, and clinical studies, the Applicant plans to use the information in the Humira® prescribing information (PI) to prepare the SB5 PI. However, as the Applicant will not seek approval for pediatric indications of SB5, pediatric indications from the Humira® PI will not be included in the SB5 PI.

In addition to pediatric indications, appropriate changes regarding SB5’s available dosage forms and strengths and presentations will be reflected in the SB5 PI. Also, to minimize the risk of potential off-label use in the pediatric patients, the Applicant plans to include the statement (b) (4) under Section 8.4 Pediatric Use of the SB5 PI and in the SB5 Medication Guide. Does the Agency agree?

FDA Response to Question 11:

We do not agree. Under the Pediatric Research Equity Act (PREA), (see section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)), all applications for new active ingredients, new indications, new dosage forms, new dosing requirement, 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(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

Because you intend to seek licensure of your proposed biosimilar product for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and psoriasis in adults, you are required to address PREA for these indications. As discussed in FDA's draft guidance on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, if the labeling for the reference product contains adequate pediatric information (information reflecting an adequate pediatric assessment) with respect to an indication for which a biosimilar applicant seeks licensure in adults, the biosimilar applicant may fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification under the BPCI Act for extrapolating the pediatric information from the reference product to the proposed biosimilar product. In addition, you will need to develop a formulation and presentation that meets the statutory standard for biosimilarity and supports dosing and administration in pediatric patients with lower body weights. Please see "PREA Requirements" in Section 3.0 below for additional information.

Discussion to Question 11:

Please refer to slide 29 in Section **6.0 ATTACHMENTS AND HANDOUTS** and to the email communication from Samsung to the FDA on June 15, 2016. We note that at the time of the meeting package you had no plans to seek approval for pediatric indications for SB5. We note your revised plan to seek licensure for the pediatric populations that would be able to utilize a 40 mg dose based on weight at the time of the initial submission. Specifically, you plan to seek approval for JIA (≥ 30 kgs) at the time of the initial BLA submission.

We will provide additional feedback on your proposed pediatric plan in the review of your iPSP.

Question 12:

The Applicant intends to claim for SB5 all adult therapeutic indications currently authorized for the reference product, Humira® based on extrapolation. However, due to business reasons (such as orphan or third party IP exclusivity, etc.) applicable to certain indications of the reference product, the Applicant proposes to use a disclaimer labeling for marketing and commercialization of SB5. Does the Agency agree?

FDA Response to Question 12:

We will provide comments on draft proposed labeling during review of the BLA.

Discussion to Question 12:

No discussion.

Question 13:

The Applicant plans to compose an eCTD application based on the core structure as outlined below. Does the Agency have any comments?

In addition, the Applicant requests the Agency's opinion on the following questions.

- a) The Applicant plans to include the Phase I CSR in Section 5.3.3 Reports of Human Pharmacokinetic (PK) Studies. The Applicant also plans to include the Phase I CSR from comparative PK study between PFS and AI in Section 5.3.1 Reports of Biopharmaceutic Studies. Does the Agency agree with this approach?*
- b) The Applicant is currently conducting an open-labelled Phase II study with an uncontrolled arm to evaluate the comparability of injection site pain between subcutaneous administration of SB5 via Safety PFS vs. AI. The Applicant plans to include the Phase II CSR in Section 5.3.5.2 Study Reports of Uncontrolled Clinical Studies. Does the Agency agree with this approach?*
- c) The Applicant plans not to include Case Report Forms in the eCTD (Section 5.3.7). Case Report Forms will be available upon request. Does the Agency agree with this approach?*
- d) The Applicant is developing SB5 as both Safety PFS and AI presentations. The Applicant plans to include information applicable to the AI presentation in Section 3.2.R Regional Information. This information supporting the AI presentation includes the following, but not limited to: development of AI including design verification test and process validation, manufacture, control, functional stability study of the AI, and human factors study. Does the Agency agree with this approach?*

FDA Response to Question 13:

- a) The bioanalytical results of pharmacokinetics and immunogenicity data should be summarized in Module 2.7.1, whereas the summary of pharmacokinetic and immunogenicity data should be located in Module 2.7.2. The analytical validation and study reports for individual studies should be in Module 5.3.1.4. The full CSRs and the associated case report forms and "DataAnalysis Data" of biopharmaceutic and human pharmacokinetic studies should be placed in Modules 5.3.1 and 5.3.3, respectively.
- b) Your plan to include the "Phase 2" AI CSR in Section 5.3.5.2 (Study Reports of Uncontrolled Clinical Studies) appears reasonable.
- c) We do not agree with your plan not to include Case Report Forms (CRFs). In the 351(k) BLA, provide CRFs and narratives for all deaths, SAEs, AEs leading to discontinuation/withdrawal, and AEs of special interest.

- d) The human factors related information should be placed in eCTD section 5.3.5.4 – “Other study reports and related information.” We note that limited information regarding the prefilled syringe and autoinjector is provided in this briefing package and it is difficult to comment on your overall approach. We refer you back to our previous Advice Letters dated November 25, 2014, January 29, 2014, October 23, 2015, and March 18, 2016 with additional information regarding our expectations for the data needed to support the proposed prefilled syringe and autoinjector devices. We also recommend that you provide a device reviewer guide with hyperlinks to the location of documentation within your future marketing submission. In addition, we recommend you provide data to support the relevance of the human factors data to the US population, such as whether the instructions were in English.

Discussion to Question 13:

The Sponsor was informed to provide the device-related information such as manufacturing, control, and functioning stability information in Section P of the eCTD.

Question 14:

Confirmation of whether the FDA requests for deletion of HS from iPSP or if the Applicant can extrapolate pediatric information from the reference product label, is based on provision of sufficient scientific justification to support a determination of biosimilarity, as is with other indications under unexpired orphan exclusivity (previously communicated to the FDA).

FDA Response to Question 14:

We confirm that HS should be excluded from the iPSP and your application. Humira is now indicated for hidradenitis suppurativa and has received orphan drug exclusivity for that indication. Your proposed product cannot be licensed for hidradenitis suppurativa until the orphan drug exclusivity expires. Once you remove reference to the hidradenitis suppurativa indication from your application and iPSP, PREA will not apply for this indication for your proposed product.

Discussion to Question 14:

Please refer to slide 28 in Section **6.0 ATTACHMENTS AND HANDOUTS**. Additionally, please refer to the discussion for Question 10 above and to the FDA communication to Samsung, “Post Meeting Comments for iPSP,” dated May 17, 2016, an excerpt of which is provided below.

You should remove reference to the hidradenitis suppurativa indication from your application and iPSP. Humira is now indicated for hidradenitis suppurativa and has received orphan drug exclusivity for that indication. Your proposed product cannot be licensed for hidradenitis suppurativa until the orphan drug exclusivity expires. Once you remove reference to the hidradenitis suppurativa indication from your application and iPSP, PREA will not apply for this indication for your proposed product.

Question 15:

Confirmation of whether the Applicant needs to provide a plan and timeline for the development of the pediatric presentations when the Applicant has already stated in the iPSP that the Applicant will submit SB5 BLA seeking licensure only for the adult indications approved for US Humira and that the Applicant currently has no specific pediatric formulation development plan for SB5.

FDA Response to Question 15:

We confirm that a plan and timeline for the development of pediatric presentations should be provided in the iPSP. See FDA's response to Question 11.

Discussion to Question 15:

Please refer to slide 33 in Section **6.0 ATTACHMENTS AND HANDOUTS**. Samsung stated their intent to submit a plan and timeline in their iPSP by the end of May 2016.

Post Meeting Comments:

1. We refer you back to our previous Advice Letters dated March 18, 2016 with additional information regarding our expectations for CMC quality microbiology data needed for the BLA.
2. Rationale for FDA-recommended Similarity Margin:

We currently recommend that the similarity margin for a comparative clinical study (CCS) in rheumatoid arthritis of a proposed biosimilar to Humira be no greater in magnitude than $\pm 12\%$. The recommended margin of $\pm 12\%$ is based on considerations aimed at weighing the clinical importance of various differences in effect against the feasibility of different study sizes. We also recommend the use of a margin based on the absolute difference scale, as this scale is considered important from a clinical perspective for an evaluation of benefit-risk in clinical trials in RA, and is typically used and well-understood as a metric to compare ACR20 responses.

FDA generally expects the type I error rate of a test of similarity to be controlled at 5%, i.e., the null hypothesis may be rejected if the 90% confidence interval (CI) for the difference in ACR20 response probabilities is contained within the similarity margin. In a CCS designed with 90% power to reject absolute differences greater than 12% in magnitude, observed differences larger than approximately 6% will result in failure to establish similarity. Therefore, the comparative clinical study will be able to rule out losses in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and will be able to rule out losses greater than around 6% with moderate (at least 50%) statistical confidence. The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of approximately 50–60% of conservative

estimates of treatment effect sizes relative to placebo for Humira (at Week 12 or 24). These estimated effect sizes were calculated from the lower bounds of 95% CIs based on meta-analyses of historical clinical trials in patients with active RA despite treatment with methotrexate (e.g., see Table 1 below). Ruling out the proposed $\pm 12\%$ similarity margin with 80–90% power under equality will likely require approximately 550–750 patients, depending on assumptions and statistical methodology. We may consider a proposal for a relaxed upper bound as part of an asymmetric similarity margin (e.g., -12%, +15%) if there is adequate justification for such an approach and for the margin chosen.

Table 1. Historical Effect of Humira on ACR20 Response¹ in Randomized Clinical Trials of Patients with Active RA Despite Treatment with Methotrexate (MTX)

Study	Week	MTX + Placebo		MTX + Humira		Difference in % Response
		N	% Response	N	% Response	
Keystone et al. ²	12	200	25%	207	57%	33%
Weinblatt et al. ³	12	62	23%	67	66%	43%
Kim et al. ⁴	12	63	25%	65	57%	32%
Chen et al. ⁵	12	12	33%	35	54%	21%
Meta-Analysis (fixed effects ⁶): Difference (95% CI)						34.0% (27.1%, 40.8%)
Meta-Analysis (random effects ⁷): Difference (95% CI)						34.1% (27.3%, 41.0%)
Heterogeneity p-value						0.54

¹ ACR20 response probabilities at Week 12 estimated based on graphical displays in Keystone et al., Weinblatt et al, and Kim et al. publications

²Keystone, E. C., Kavanaugh, A. F., Sharp, J. T., Tannenbaum, H., Hua, Y., Teoh, L. S., ... & Chartash, E. K. (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. *Arthritis & Rheumatism*, 50(5), 1400-1411.

³ Weinblatt, M. E., Keystone, E. C., Furst, D. E., Moreland, L. W., Weisman, M. H., Birbara, C. A., ... & Chartash, E. K. (2003). Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis & Rheumatism*, 48(1), 35-45.

⁴KIM, H. Y., LEE, S. K., SONG, Y. W., YOO, D. H., KOH, E. M., Yoo, B., & Luo, A. (2007). A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR Journal of Rheumatology*, 10(1), 9-16.

⁵Chen, D. Y., Chou, S. J., Hsieh, T. Y., Chen, Y. H., Chen, H. H., Hsieh, C. W., & Lan, J. L. (2009). Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in

combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. Journal of the Formosan Medical Association, 108(4), 310-319.

⁶ Based on Mantel-Haenszel weights

⁷ Based on DerSimonian-Laird approach

3. Post-Meeting Note regarding the submission of a proper name for SB5:

FDA recommends that Samsung submit 3 proposed suffixes, listed in your order of preference, composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at such time as Samsung's proposed biosimilar to Humira may be licensed. Samsung's proposed suffixes should be devoid of meaning and follow the recommendations for proposed suffixes in section V of FDA's draft guidance on Nonproprietary Naming of Biological Products (see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>).

In addition, given that FDA requested comment in the Notice of Availability for the draft guidance (80 FR 52296, August 28, 2015) on, among other things, the potential benefits and challenges of designating a suffix in the proper name of a biological product that devoid of meaning versus meaningful (e.g., a suffix derived from the name of the license holder), Samsung also may consider proposing 3 additional suffixes that are meaningful (e.g., derived from the name of the prospective license holder) and composed of four lowercase letters. These additional suffixes also should be listed in your order of preference in your submission.

Samsung should include the proposed suffixes in their original 351(k) BLA, along with any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in the draft guidance. FDA will notify Samsung of the suitability of the proposed suffix upon completion of the Agency's evaluation.

3.0

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to initiating your comparative clinical study (see additional comments below regarding expected review timelines).

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

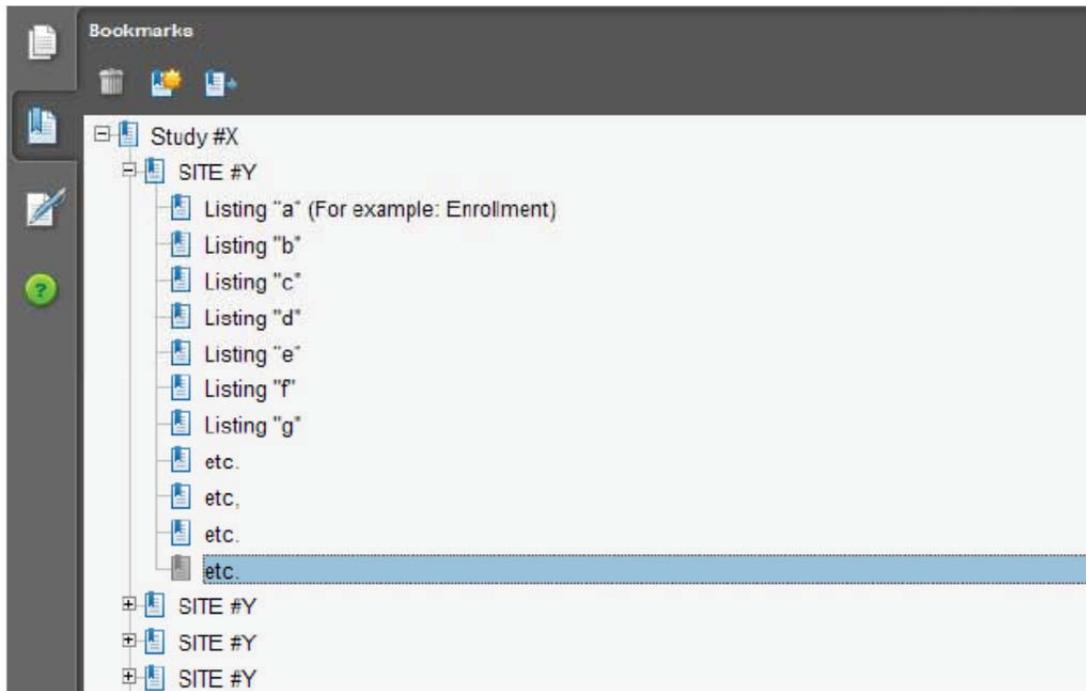
1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location 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.

2. Please include the following information in a tabular format, *by site*, in the 351(k) BLA for each of the completed clinical studies:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each clinical study: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation

- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the clinical studies)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each clinical study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No further issues remain for discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Please find attached Samsung slides presented/discussed at the May 4, 2016 meeting.

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

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/s/

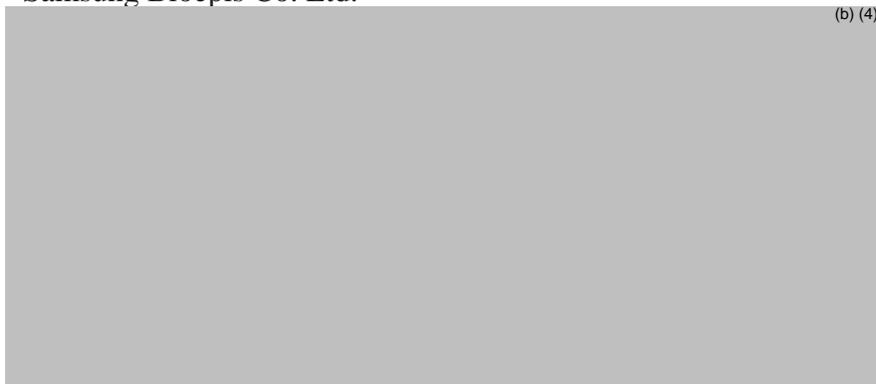
JESSICA K LEE
06/23/2016



PIND 118299

MEETING MINUTES

Samsung Bioepis Co. Ltd.



Please refer to your Pre-Investigational New Drug Application (PIND) file for SB5.

We also refer to the meeting between representatives of your firm and the FDA on July 3, 2013. The purpose of the meeting was to discuss the CMC, nonclinical, clinical and medical device development plan of SB5 as a proposed biosimilar to US-licensed Humira.

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

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: Biosimilar Biological Product Development (BPD) Type 2

Meeting Date and Time: July 3, 2013 at 1:00 Pm – 2:30 PM
Meeting Location: FDA White Oak, Building 22, Room 1313

Application Number: 118299
Product Name: SB5 (proposed biosimilar to Humira)
Indication: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps).

Sponsor Name: Samsung Bioepis Co.
(b) (4)

Meeting Chair: Badrul A. Chowdhury, MD, PhD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Sarah Yim, MD, Associated Director, DPARP
Janet Maynard, MD, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Laurie Graham, PhD, Biologist, Division of Monoclonal Antibodies
Jun Park, PhD, Biologist, Division of Monoclonal Antibodies
Timothy Robison, PhD, Pharmacologist Team Leader, DPARP
Andrew Goodwin, PhD, Pharmacologist, DPARP
Ping Ji, PhD, Clinical Pharmacology Reviewer, DCPII
Joan Buenconsejo, PhD, Lead Mathematical Statistics, Division of Biometrics II
Yongman Kim, PhD, Mathematical Statistics, Division of Biometrics II
Jessica Lee, PharmD, Regulatory Project Manager, DPARP
Jay Sitlani, J.D., Senior Regulatory Counsel, Office of Regulatory Policy (ORP), Division of Regulatory Policy I (DRPI)
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics, Therapeutic Biologics and Biosimilars Team (TBBT), Office of New Drugs (OND)
Sue Lim, M.D., Senior Staff Fellow, TBBT, OND
Neel Patel, PharmD, Regulatory Project Manager, TBBT, OND
Carla Lankford, MD, PhD, Science Policy Analyst, TBBT, OND
Tyree Newman, Senior Regulatory Project Manager, TBBT, OND

Carlos Mena-Grillasca, RPh, Safety Evaluator, Division of Medication Error Prevention and Analysis

SPONSOR ATTENDEES

Hee Kyung Kim, BPH, MBA, Vice President, Regulatory Affairs

InYoung Baek, Ph.D., Director, Medical & Lifecycle safety

Jee Hoon Ghil, MD, Clinical Research Physician, Director, Medical & Lifecycle safety

Young Hee Rho, MD, Ph.D., MPH, Clinical Research Physician, Director, Medical & Lifecycle safety

Ji-Young Hong, Senior Manager, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Samsung Bioepis requested a Type 2 Biosimilar Biological Product Development meeting on April 17, 2013. The Type 2 meeting was granted May 7, 2013. The Preliminary Comments were provided to Samsung on July 2, 2013. At the meeting on July 3, 2013, Samsung provided a PowerPoint handout, which is attached in Section 6.0. Samsung questions provided in the briefing material are in italics, the FDA responses and meeting discussion are in normal font.

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

Question 1: *The applicant plans to use the (b) (4) strain as the production cell line for SB5.* (b) (4)

Does the Agency agree with this approach?

FDA Response to Question 1:

Your plans to qualify the HCP immunoassay for the (b) (4) strain appear to be reasonable. The final determination of acceptability will be a review issue.

Discussion to Question 1:

The sponsor accepted FDA's response, no discussion occurred.

Additional CMC Comments:

The preliminary analytical similarity assessment provided suggests that there are differences between SB5 and US-licensed Humira. Specifically, major differences were observed for charge variants. Other differences observed between SB5 and US-licensed Humira include glycosylation, aggregates, FcγRIIIa binding and C1q binding. These differences lead to uncertainty regarding the analytical similarity of SB5 to US-licensed Humira, and we recommend that you identify appropriate steps to address this uncertainty. It may be that minor observed differences to date were related to an insufficient numbers of lots being used in the analytical similarity studies, and these differences, therefore, would be minimized or eliminated by the inclusion of additional lots of SB5, US-licensed Humira and EU approved-adalimumab in analytical similarity studies. However, we encourage you to investigate and, if appropriate, incorporate changes to your manufacturing process that would result in a SB5 product that better matches the critical quality attributes of US-licensed Humira.

Additional studies to assess the impact of any observed differences should also be considered. Persistent differences in critical quality attributes, which are verified, may significantly impact your ongoing development program, including the ability to demonstrate that your SB5 product is highly similar to US-licensed Humira. See the draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM291128.pdf>.

Based on the brief information provided in the meeting package, we also have the following additional comments for your consideration:

- a) Your overall analytical similarity exercise should include lots manufactured by the proposed commercial process as well as lots that will be used in clinical trials in order to support a 351(k) application.
- b) Your similarity assessment should include an assessment of drug product for those attributes that are impacted by drug product manufacturing and the final container closure system. For example, the similarity exercise should include an assessment of sub-visible particles and the impact on product quality of (b) (4). In addition to measuring particulates that are $\geq 10 \mu\text{m}$ in size, subvisible particulates in the 2-10 μm range should also be characterized and quantified using technique(s) that can accurately estimate the amount of subvisible protein particulates present.
- c) The analytical similarity exercise should include a sufficient number of SB5, US-licensed Humira and EU-approved adalimumab lots. The final number of lots required will depend, in part, on the extent of lot-to-lot variability observed. Also, provide a basis for the selection of the specific lots being studied, along with the ages of the lots being compared. The US-licensed reference product lots as well as EU-approved adalimumab lots should ideally be selected across the shelf-lives of the products. Pre-specified similarity acceptance criteria should be established for all 3 comparisons (i.e. SB5 vs. US-licensed Humira, SB5 vs. EU-approved adalimumab,

- and US-licensed Humira vs. EU-approved adalimumab). The statistical basis for establishing the similarity acceptance criteria should be described in detail. For any differences observed, a risk assessment should be provided on the potential impacts on safety and/or efficacy.
- d) Your similarity assessment should include an assessment of process related impurities.
 - e) The similarity exercise should include a forced degradation study that compares the rate and pathway of degradation of SB5 to that of US-licensed Humira and EU-approved adalimumab. You should provide justification for the conditions under which the degradation profiles are assessed and for the number of lots used in the studies.
 - f) All charge variants should be identified and assessed for their impact on potency if appropriate.
 - g) Provide detailed descriptions of the proposed assays for assessment of biological activities for SB5 as part of the biological characterization to establish analytical similarity of SB5 to the reference product. In addition, provide assessment of SB5 binding affinities and specificity for TNF- α .
 - h) The extinction coefficient for both US-licensed Humira and SB5 should be determined experimentally to confirm that the biosimilar product has the same strength as the reference product. Provide information in the IND submission on the methods used to establish the extinction coefficient for SB5 and the reference product.
 - i) Analytical data from each lot should be presented in a graphical format (e.g., chromatograms, electropherograms, peptide maps, gels, bar graphs or other easy-to-read formats) in addition to the tabular format that enables direct comparison of the results from each individual lot and clearly delineates US-licensed Humira lots from lots of SB5.
 - j) Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of anti-drug antibodies (ADA) against SB5, US-licensed Humira and EU-approved adalimumab. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference. The validated assay should be capable of sensitively detecting ADA responses in the presence of the products levels that are expected to be present at the time of patient sampling. Information on the expected product levels that will be present in patient samples should be included to support use of the assay. An assay should also be developed that is able to delineate neutralizing ADA responses. Until an assay (s) has

been developed and validated, patients samples should be banked under appropriate storage conditions.

- k) Provide detailed information on the SB5 manufacturing processes for nonclinical, clinical, and to-be marketed materials. Provide data sufficient to demonstrate that the SB5 materials used for the nonclinical studies are comparable to those used for the proposed clinical studies.

Limited CMC information is provided in the pre-meeting package. Submit appropriate CMC information including safety, composition, manufacture, and control of the drug substance and drug product in the IND submission. Please refer to the 1997 FDA guidance “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use” (FDA 1997 PTC-mAb), which can be found at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153182.pdf>

Discussion to CMC Additional Comments:

Samsung presented a table in slide 4 of their handout, which is attached in Section 6.0, that described their plans to address analytical differences observed between SB5 and US-licensed Humira. It was discussed that the overall approach proposed by Samsung appeared reasonable, but that the Agency could not agree that the information provided in the table would be sufficient to address the uncertainty regarding analytical similarity between SB5 and US-licensed Humira, particularly as the briefing package only contained a portion of the proposed analytical similarity exercise. FDA suggested that Samsung provide further details including necessary chromatographs, etc.

Samsung and the FDA also discussed the methodology and plans for validation of the assays that would be used for the detection of anti-drug antibodies (ADA). Samsung plans to use a single assay to detect antibodies against SB5, US-licensed Humira, and EU-approved adalimumab (refer to Slide 5). The FDA agreed that one assay could be acceptable, if the assay was shown to have adequate performance, including sensitivity, to antibodies against all 3 products. .

Question 2: *The applicant was unable to find relevant animal models including transgenic mouse models for PD study to demonstrate similar in vivo behavior between SB5 and Humira ®. Thus, the applicant plans to focus on extensive in vitro studies including binding assays and cell based assays to demonstrate similarity in binding and biological activity between SB5 and Humira ®. The applicant believes that an in vivo PD study using an irrelevant animal model is not necessary and the planned in vitro studies are sufficient to provide non-clinical evidence of similarity between SB5 and Humira ® in place of in vivo PD studies. Does the Agency agree with this approach?*

FDA Response to Question 2:

We agree that no *in vivo* PD model (i.e., Tg197 mouse) is necessary to support the development of SB5. However, we have the following comments regarding your overall approach for the demonstration of biosimilarity between SB5 and US-licensed Humira.

As acknowledged in your briefing package, your nonclinical studies evaluating the similarity of SB5 to US-licensed Humira are incomplete and appear to only include two pilot lots of SB5. Your proposed list of *in vitro* nonclinical assays (Table III-2, Volume 1, page 67) appears reasonable. Refer to FDA's response to Question 1 for comments regarding your analytical similarity assessment program.

The totality-of-the evidence, including the analytical and nonclinical data obtained with your product in comparison to US-licensed Humira will be evaluated to determine the safety and similarity of your product to support opening your IND. Robust analytical similarity results and your ability to address any residual uncertainty regarding the similarity of SB5 to US-licensed Humira may permit a selective and targeted approach with respect to the nonclinical data package necessary to support the opening of your IND. In the absence of robust data demonstrating analytical similarity between SB5 and US-licensed Humira, we recommend a 1-month cynomolgus monkey toxicology study. Refer to the response to Question 3 for recommendations regarding study design.

A final determination regarding whether the clinical investigation may proceed will be made after submission and review of the data in the IND. The adequacy of nonclinical studies to support a biosimilar marketing application cannot be made at this stage of development. Whether further nonclinical studies will be required remains a review issue. However, if after review of data, we conclude that SB5 is similar to US-licensed Humira from a nonclinical perspective, then the reproductive toxicology, immunotoxicity, safety pharmacology and an evaluation of the carcinogenic potential (e.g., review of nonclinical studies and published scientific literature for any tissue proliferative or immunosuppressive effects associated with adalimumab) will not be needed.

Discussion to Question 2:

The sponsor accepted FDA's response, no discussion occurred.

Question 3: *Once similarity in quality and non-clinical in vitro studies is demonstrated between SB5 and Humira ®, the applicant believes that animal toxicity studies are not necessary. However, if deemed necessary, the applicant plans to perform a 4 week repeated dose toxicity study in cynomolgus monkeys to demonstrate similar in vivo behavior between SB5 and US sourced Humira ®. Does the Agency agree that the proposed study design is appropriate to demonstrate similarity in toxicity profiles between SB5 and US sourced Humira ®?*

FDA Response to Question 3:

We agree that a four-week repeat dose toxicity study in cynomolgus monkeys is appropriate, but we do not agree with your proposed dose level. We have the following recommendations regarding the study design:

We recommend a 1-month cynomolgus monkey toxicology study in males and females that receive weekly subcutaneous (SC) dosing of vehicle control, SB5 or US-licensed Humira. A SC dose of ≥ 70.9 mg/kg/week for SB5 and US-licensed Humira is recommended to link to a known pharmacodynamic effect or anticipated toxicity. We recommend 3 animals/sex/group and no recovery group is needed. An assessment of pharmacokinetics, immune cells (i.e., immunohistochemistry or immunophenotyping assay) and a standard histopathology evaluation should be incorporated into the study. An additional vehicle control group for SB5 relative to the reference product may be needed if safety issues are identified for the excipients in your product (i.e., a novel excipient or one not used in an approved product administered via the SC route).

The FDA strongly supports a risk-based approach to determining the necessity of animal studies to support opening an IND for a biosimilar development program. The lack of sufficient analytical similarity data at this time has resulted in an assessment of high risk leading to the advice to conduct a 4-week monkey study with SB5 and the reference product. Note that if sufficient analytical similarity data had been provided, a different assessment of risk may have been made, leading to different advice regarding your nonclinical program intended to support opening your IND.

Discussion to Question 3:

Samsung requested clarification on FDA's recommendation to use a ≥ 70.9 mg/kg/week subcutaneous (SC) dose for SB5 and US-licensed Humira. Samsung contended that the proposed dose of 32 mg/kg is 18 to 48 times greater than the clinical dose, which they consider to be sufficient to demonstrate the safety of SB5 relative to US-licensed Humira. The safety margins are consistent with the recommendations in the ICH S6 (R1) Guidance. Finally, Samsung noted difficulties in purchasing sufficient amounts of the US-licensed reference product for the study and doubling the dose would increase this problem. The FDA clarified that the recommended SC dose ≥ 70.9 mg/kg/week was not a matter of a safety margin, but was highly recommended in order to allow a pharmacodynamic comparison of immunohistochemical changes in the spleen induced by SB5 and the reference product, US-licensed Humira. However, FDA clarified that the SC dose ≥ 70.9 mg/kg/week was a recommendation from the FDA and dose selection was ultimately Samsung's decision. FDA noted that adequate justification should be provided by Samsung to support the dose used.

Question 4: *The applicant plans to conduct a randomized, single-blind, three-arm, parallel group, single-dose pharmacokinetics (PK) study in healthy subjects to demonstrate similarity in PK profiles of SB5, US sourced Humira ® and EU sourced Humira ®.*

- A. *Does the Agency agree that the study is appropriately designed to demonstrate similarity in PK profiles? (refer to Annex 1 – Clinical Study Protocol Synopsis for Phase 1)*
- B. *The frequency of anti-adalimumab antibody (AAA) positive samples is known to vary highly in Humira ® pharmacokinetic studies. Therefore, the applicant proposes to use AUC_{0-336} as the primary endpoint instead of AUC_{last} and AUC_{inf} , when both parameters*

show significant difference between subjects with and without AAA. Does the Agency agree with this approach?

- C. *A sample size of 60 subjects per arm in the three arm parallel PK study was calculated, given an equivalence margin of 0.8 – 1.25, 5% difference in true geometric means of pharmacokinetic endpoints between SB5 and Humira ®, a between-subject standard deviation of 0.33, and a 90% power requirement. Does the Agency agree that this statistical justification is acceptable?*

FDA Response to Question 4:

Yes, we agree that the study design and the sample size justification are appropriate. However, we do not agree that AUC₃₃₆ should be used as the primary endpoint, which would replace AUC_{last} and AUC_{inf} if anti-adalimumab antibody (AAA) was significant. We do not recommend the use of AUC₃₃₆ in place of AUC_{inf} to assess PK similarity, as AUC₃₃₆ cannot represent AUC_{inf}. Furthermore, as a biosimilar, it would be anticipated that any differences in the SB5 arm between AUC_{inf} and AUC₃₃₆ due to AAA would be similarly observed in the US-licensed Humira and EU-approved adalimumab arms.

We note that you are proposing to conduct this study in male healthy volunteers only. We recommend that you include female volunteers as well.

Discussion to Question 4:

Samsung presented a summary of the PK studies conducted to support the licensure of Humira in slide 11 of the handout, found in Section 6.0. Samsung stated that these studies did not show gender differences and therefore Samsung proposed to enroll healthy male volunteers in their PK similarity study, and to enroll female and male RA patients in their comparative clinical study.

FDA reiterated that because the available data did not demonstrate any gender differences, they recommend that both male and female volunteers be enrolled in the PK similarity study. To address Samsung's concern regarding exposure to TNF- α inhibition during pregnancy, FDA suggested that the inclusion criteria be tightened, such as enrolling women with no child-bearing potential, in order to reduce the potential risk.

FDA also clarified that the population PK data collected from the comparative clinical study would not be used to demonstrate PK similarity.

Samsung also requested clarification regarding the necessary sampling period. FDA stated that sampling for 3-5 half-lives should be done and recommended a period of 70 days to cover 80% of AUC_{inf}.

Question 5: *The applicant plans to conduct a randomized, double-blind, parallel group, multicenter Phase 3 clinical study to evaluate the efficacy, safety, tolerability and immunogenicity between SB5 and EU sourced Humira ® in subjects with moderate to severe RA. Does the Agency agree that the design of the proposed Phase 3 study in subjects with*

RA reflecting the time-response model as supportive analysis is appropriate to demonstrate similarity in efficacy and safety profiles between SB5 and Humira ® in support of a 351(k) for SB5 as a biosimilar product to Humira ®?

FDA Response to Question 5:

The purpose of a comparative clinical study in a biosimilar development program is to address residual uncertainties about biosimilarity between the proposed biosimilar and reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. Ideally, if a stepwise approach is taken, the need for and design of additional clinical studies would be tailored to evaluate and address the potential clinically meaningful differences of any residual uncertainty. However, it is difficult to anticipate what residual uncertainties, if any, would arise from yet to be conducted structural and functional characterization, animal testing, human PK and PD studies, and clinical immunogenicity assessment, and furthermore what clinical concerns those uncertainties would raise. As a result, FDA has been encouraging pursuit of clinical trial design features that would provide the most sensitivity to detect any clinically meaningful differences.

In the absence of sufficient analytical, animal, clinical PK and PD, and other data for SB5, we remain concerned whether your trial as currently designed is adequately sensitive to detect clinically meaningful differences between products, if they exist.

You propose a clinical efficacy trial in RA with an equivalence design, using ACR20 as the primary endpoint at Week 24. Such a trial would not be expected to be able to discriminate between products, as products with completely different mechanisms of action would likely yield similar results, using approved doses.¹ If, however, you can justify based on analytical, animal, PK and PD, and other data or information, that only minimal residual uncertainty exists, then the general design features of the trial you proposed could be adequate to (1) demonstrate no clinically meaningful difference between SB5 and US-licensed Humira, with incorporation of a single transition as discussed below in Question 6, and (2) support extrapolation to other conditions of use.

Furthermore, we note that you intend to use EU-approved adalimumab as the comparator in your comparative clinical study. In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. However, you may use a non-US-licensed comparator product (EU-approved adalimumab) in certain studies to support a demonstration that SB5 is biosimilar to Humira, the US-licensed reference product. If you seek to use data from nonclinical or clinical studies comparing SB5 to EU-approved adalimumab to support, in part, the requirements under section 351(k)(2)(A) of the PHS Act, you should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and establish an acceptable scientific bridge to the US-licensed reference

¹ Demin et al. *Clin Pharm & Ther.* Sept 2012; 92(3):352-359; and Samsung's analysis per the SB5 briefing document.

product. The type of bridging data that may be needed to provide adequate scientific justification for this approach would likely include a bridging PK study, in addition to direct physicochemical characterization between all three products. All 3 comparisons (SB5 to US-licensed Humira, SB5 to EU-approved adalimumab, and EU-approved adalimumab to US-licensed Humira) should meet the pre-specified acceptance criteria for analytical and PK similarity.

Discussion to Question 5:

Samsung provided data (slides 12 and 13) and stated they believed their time-response modeling method was sensitive enough to discriminate treatment effect between products, and requested clarification if their proposed comparative clinical study design was acceptable. The FDA responded that the time-response model may be more sensitive compared to an analysis using a single time point, but they also noted that there were potential limitations to the time-response model, as described in previous communications (refer to the meeting minutes from the December 7, 2012 meeting and the May 29, 2013 communication under PIND 113461) to Samsung. The FDA added that it was difficult to comment further at this stage because of residual uncertainty that could arise from yet to be conducted studies (e.g., analytical and clinical PK).

Samsung asked the FDA if the full analysis set (based on the intent-to-treat principle) with the method of last observation carried forward or any other missing imputation method for missing values could be used. The FDA recommended that the analyses be conducted in both per-protocol and intent-to-treat populations. Further, handling of missing data needs to be pre-specified and justified in the protocol and analysis plan.

Additional Comment:

FDA reminds sponsors that the Investigator Brochure should be carefully prepared to ensure that it is not misleading, erroneous, or materially incomplete, which would be the basis for a clinical hold (see 21 CFR 312.42(b)(1)(iii) and (b)(2)(i)). For example, the Investigator Brochure should avoid conclusory statements regarding regulatory determinations (e.g., “comparable,” “highly similar,” “biosimilar”) that have not been made. It would be acceptable to state that “SB5” is a “proposed biosimilar product,” but not a “biosimilar product.” Where appropriate, you may describe the results of comparative studies using appropriate descriptive terms that are not closely associated with regulatory determinations (e.g., the term “similar” may be acceptable; however, the terms “highly similar” or “biosimilar” would not be acceptable.

Question 6: *The applicant proposes to investigate safety and immunogenicity upon transitioning from Humira® to SB5 as part of a Phase 3 study. At Week 24 subjects receiving Humira® will be randomized in a 1:1 ratio to either continue to receive Humira® or transition to SB5 until Week 52. Does the Agency agree that the proposed design is appropriate to demonstrate similarity in safety profiles between SB5 and Humira®, and also to evaluate the safety and immunogenicity profiles of subjects transitioning from Humira® to SB5?*

FDA Response to Question 6:

You should assess safety and immunogenicity in the setting of patients who undergo a single transition from the EU-approved comparator product to the proposed biosimilar to provide a descriptive comparison with patients who continue on the EU-approved comparator product. Such an assessment could be incorporated as modifications to your currently proposed trial or as a separate study. We also recommend that you pre-specify windows of attribution for adverse events regarding the specific study drug, as well as pre-specified events of special interest, including anaphylaxis and hypersensitivity reactions.

In your development program, you should enroll an adequate number of subjects to have a descriptive sense of whether transitioning from adalimumab to SB5 would result in a major risk in terms of hypersensitivity reactions, including anaphylaxis, immunogenicity, or other reactions. This information would need to be provided with the original BLA submission. In principle, your proposal to randomize 245 patients to either continue EU-approved adalimumab or be transitioned to SB5 at week 24 up to week 52 appears reasonable.

Discussion to Question 6:

Samsung wanted clarification of the concept of “windows of attribution.” The FDA clarified that it was a general statement rather than specific to the transition from EU-approved adalimumab to SB5. The “window of attribution” refers to the period after the last dose of study drug during which the subject should be monitored for adverse events that would still be attributable to the drug.

Question 7: *In relation to Question 6, the applicant proposes to investigate safety and immunogenicity in subjects transitioning from Humira® to SB5 after 16 weeks, which is considered sufficient to assess the immunological response of adalimumab. Does the Agency agree that the proposed evaluation period of 16 weeks is acceptable?*

FDA Response to Question 7:

See response to Question 6.

Discussion to Question 7:

Samsung presented justification for a 16-week evaluation period for immunogenicity after the single transition from EU-approved adalimumab to SB5. The FDA stated that Samsung’s plan appeared to be reasonable.

Question 8: *Once similarity between SB5 and US sourced Humira® has been demonstrated through extensive quality similarity exercises, a series of non-clinical studies, a PK study in healthy subjects and a Phase 3 study in RA subjects, there is no reason to expect any differences in safety, purity and potency between SB5 and Humira® in other patient populations for which Humira® is indicated. Does the Agency agree that the proposed biosimilar, SB5 can be licensed for all other indications for which Humira® is licensed?*

FDA Response to Question 8:

If SB5 meets the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for SB5 to be licensed for one or more additional conditions of use for which the reference product is licensed. You would need to provide sufficient scientific justification for extrapolating clinical data to support the determination of biosimilarity for each condition of use for which you seek licensure.

A scientific justification for extrapolation of clinical data in one condition used to support licensure in one or more additional conditions of use for which the reference product is licensed should address, for example, the following issues for the testing and extrapolating conditions of use:

- The mechanism of action in each condition of use which licensure is sought; this may include:
 - The target/receptor(s) for each relevant activity/function of the product
 - The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors
 - The relationships between product structure and target/receptor interactions
 - The location and expression of the target/receptor(s)
- The pharmacokinetics and biodistribution of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities)
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought.

Discussion to Question 8:

The sponsor accepted FDA’s response, no discussion occurred.

Question 9: *The applicant proposes to submit a biological license application of the proposed biosimilar, SB5 under section 351(k) of the Public Health Service Act (PHS Act) with a complete quality, non-clinical and Phase 1 data in healthy subjects, and the 40 weeks data of Phase 3 study including transition study results. In addition, the applicant will commit to submit the final 52 weeks data of Phase 3 study during 351(k) application review (at the time of D120 safety update submission). Does the Agency agree with this approach?*

FDA Response to Question 9:

It is premature to comment on the content of a BLA for your proposed product, SB5, at this stage of development. We refer you to our responses to the questions you posed in your meeting package providing advice and feedback on your proposed development program. We note the following points for your consideration:

1. Regional differences in clinical practice may affect the applicability of the study results conducted in sites outside of the US to the US population. You will need to provide justification that the results from your comparative clinical study can be extrapolated to the US population.
2. We remind you that the application should be complete at the time of the original submission.
3. We strongly recommend that you conduct the comparative clinical study with the to-be-marketed formulation.

Discussion to Question 9:

Samsung asked, if the study was conducted outside of the US, what study population would be considered to be representative of the US population in the comparative clinical study. The Agency clarified that there will likely be differences in clinical practice (e.g., standard of care) and the resultant clinical experience of patients in different countries. FDA was not recommending a specific study population per se but a population that shared a similar clinical experience to that of patients in the United States. Samsung will need to provide justification as noted in the response to Question 9.

Question 10: *The applicant plans to develop SB5 in a prefilled syringe (PFS) presentation. In addition, the applicant is considering to develop SB5 as an autoinjector device designed for self-injection by patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis.*

- A. *The applicant plans to perform human factor validation testing in subjects with RA, PsA, AS as well as in healthcare providers using an injection pad. Does the Agency agree that the testing is appropriately designed to demonstrate that intended users of the autoinjector can safely and effectively perform critical tasks for the intended use in the expected use environment?*
- B. *Once equivalence between the autoinjector device and PFS is demonstrated through comprehensive data and justification regarding technical characteristics that could affect the drug and/or drug delivery, the applicant believes that a clinical PK study to demonstrate equivalence between PFS and autoinjector device is not necessary. Does the Agency agree with this approach?*

FDA Response to Question 10:

Response to Question 10A:

We agree that a simulated use human factors design validation study is acceptable. However, we do not agree that the testing is appropriately designed to demonstrate the product meets user needs and the intended use of the product. We recommend that you conduct a comprehensive risk analysis identifying the use-related risks with this autoinjector. The purpose of a human factors study is to demonstrate that the device can be used by

representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

We ask that you explicitly demonstrate that all of the use-related risks for this combination product have been successfully mitigated. In this capacity, if you utilize existing testing (i.e. testing from previous BLA submissions where this particular autoinjector was the device constituent) to demonstrate the safe and effective use of the autoinjector, then you should clearly explain how this testing mitigates the specific use risks as associated with the autoinjector. However, if we disagree on whether the existing testing appropriately addresses a particular use-related risk, you may have to perform additional testing to demonstrate that the use-related risks associated with this combination product have been mitigated.

We request that you submit the draft protocol and Instructions for Use (IFU) prior to initiating the simulated use validation study. Additionally, we seek clarification on the following.

1. You propose to test 3 distinct user groups that include Rheumatoid Arthritis (RA) and/or Psoriatic Arthritis (PsA) patients, caregivers, and healthcare professionals. Clarify whether or not these user groups will receive training prior to conducting the test. We recommend an untrained arm for each distinct user group.
2. You stated that your study will include 75 participants representing RA patients and/or PsA patients, non-professional caregivers, and healthcare professionals. We are unclear why only RA and PsA patients will be recruited for the study given that the indications cover other patients with other disease conditions. Please clarify.
3. Confirm the injection pad will be placed at the intended site of administration to simulate real world use.
4. You propose to use objective and subjective assessment of all use errors, close calls and near misses. Clarify how you intend to collect and analyze this data. We request that you include open ended interview questions directed towards any failure or close calls that users experience while using the device. The use of open ended questions provides qualitative data that can provide insight into how and why participants may have difficulty with the device and IFU.
5. Describe the methods you will use to detect use errors, close calls, and near misses following completion of a given hands-on task. We request you also include the following in your data collection of user errors, close calls and near misses:
 - Malfunctioning of the autoinjector during administration
 - Patients attempting to inject using the wrong end of the injector. Include information on needle stick injury
 - Solution present at the site of injection during administration or after the injection is complete

- Patients removal of the device prior to the allotted time for administration of this product
 - Patients not applying sufficient pressure to fire the autoinjector
6. Describe how the critical or primary tasks for this product will be selected for testing. Additionally, we request the following to be included as critical tasks:
- Participants identify the correct site of injection and complete the injection.
 - Participants held the injection for the allotted time for administration of the product.
 - If audible sounds or visual cues are present, the participant understands and utilizes these cues appropriately.
7. Confirm that the device used in the study is the same as what will be used in the commercial market.
8. Provide a description of the simulated use testing environment and discuss how that environment represents actual use environment.
9. There is other information that we need to review such as use-related risk analysis, devices and labeling that will be used in the study, training, data collection and analyses, etc. We recommend that you submit a complete study protocol along with a use related risk analysis for review and comments prior to conducting the study. Ensure that your protocol includes discussion on the following elements as well:

Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials. In addition, to establish the scope and facilitate understanding of the testing you perform, provide a graphical depiction of the user interface for your device. Explain the overall interaction between users and the user interface and refer to it as necessary when discussing task priority, specific test results or residual risk.

A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing. Based on your analysis of your intended users and the use of your device, you should determine the extent and type of training needed and indicated for users prior to using your device. After the training need is established and the training materials prepared, you should train the user participants for your human factors/usability validation testing in the same manner that actual users will be trained. You should provide at least some lag time between training and the testing. When you design your human factors/usability validation protocol, include this analysis and ensure that representative (i.e., realistic) training is given to all test participants. Describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, we expect that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

User Tasks and Use-Related Risks Analysis

We expect to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Describe all activities in which your test participants will engage during the test.

In addition, for human factors/usability validation testing, we need to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.

Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing. Aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Evaluate the use of your device under whatever conditions you identify as potentially occurring and hazardous.

Describe the testing environment and realism of the simulated use in sufficient detail and justify how they were appropriate for validation testing.

Study Participants

You should include as many representative users in your human factors/usability validation as your analysis indicates are necessary to achieve a reasonable validation. We expect the number of study participants to be used in Human Factors/Usability Validation to be a minimum 15 per user group. Plan to submit results of a study that includes a minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g. level of disabilities/impairments) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25.

Regardless of the number of groups you test, provide a rationale that these groups are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

For devices sold in the United States, we have consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

Realism of simulated use

The testing environment and realism of the simulated use was not described in sufficient detail to determine if it is reasonable for a validation study of device use, however a “focus group” approach is not likely to represent actual use conditions. Determine the conditions under which the testing will be undertaken and include realistic and challenging scenarios of use that, in aggregate, include all critical user tasks which you have identified.

Data Collection and Analysis

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim, that your device can be used safely and effectively by the indicated users. We expect you to collect both empirical and qualitative data in a design validation study.

User Performance Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants’ adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Subjective Data – We expect you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant. Your data analysis should be prioritized based on identified risk and task priority (from highest to lowest) to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

Discussion to Question 10A:

The sponsor accepted FDA's response, no discussion occurred.

Response to Question 10B:

No, we do not agree that equivalence between the autoinjector (AI) device and PFS based on comprehensive data and justification regarding technical characteristics is adequate. To support the AI you will need to provide additional data. Additional data required to support licensure of prefilled syringe and autoinjector combination products would include, among other things, demonstration 1) that the drug/device results in the desired delivery of drug to the intended biospace in the intended population (i.e., clinical data, which might include PK and/or efficacy); and 2) the device has adequate design verification, validation, and robustness (e.g., functional bench testing to assess the operational performance of the device,

human factors testing, actual use device robustness testing and label comprehension studies). As patients with inflammatory hand arthritis may have impaired dexterity, we recommend that the PK study be conducted in a representative patient population. If PK across a spectrum of body weights is similar between the PFS- and AI- administered products, then it is possible that no further clinical trials would be needed to support approval of SB5 in an autoinjector presentation. We also recommend that all devices be collected after use in this study and examined for any evidence of failure.

For guidance on human factors assessments, refer to the FDA document, "Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management"
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM094461.pdf>.

The device used for delivery of a biological product may impact consideration whether that product would meet the statutory requirements for a proposed biosimilar biological product under section 351(k) of the PHS Act. Thus, you would need to provide product- and device-specific information to the IND or to cross-reference IDE, PMA, 510k, or Device Master File to support the assertion that the proposed PFS or autoinjector presentation of your biological product would meet the statutory standard for biosimilarity to the reference product (US-licensed Humira). Each container closure system (prefilled syringe or autoinjector) should be demonstrated to be compatible for use with the drug product (DP) in the final formulation. Therefore, extractable/leachable studies should be performed with all parts of the container/closure that come in direct contact with the product.

In addition, stability studies with the drug product in each container/closure system should be performed at the proposed storage temperature, as well as at accelerated and stressed conditions. We also strongly recommend that you use the intended commercial container closure system in the pivotal trials. Please refer to FDA guidance for industry document: "Container-Closure Systems for Packaging Human Drugs and Biologics," May 1999.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070553.pdf>.

Additional Comments:

Prefilled Syringe

We note that you are also proposing a prefilled syringe to be used for this product. Submit an IFU for the proposed pre-filled syringe.

Discussion to Question 10B:

Samsung plans to market an autoinjector (AI) that will be launched simultaneously with the prefilled syringe (PFS). The PFS is the presentation Samsung will use in the clinical studies. Samsung plans to establish similarity between the AI and PFS through the human factor and relevant functional studies. Samsung requested clarification if, based on the proposed data

package, additional clinical data (i.e., PK study) comparing the PFS and AI would still be necessary. The Agency reiterated that, because the PFS is used in the clinical studies, it would be important to demonstrate that product delivery is not affected with use of the AI. Demonstration of similar PK would reflect that the same amount of product is being delivered to the intended biospace. The Sponsor could consider the most appropriate population for this PK study. Healthy volunteers might be reasonable, or the evaluation could be incorporated into the human factors study in patients. However, FDA noted that if the PK study was conducted in healthy volunteers, the sponsor would still need to address use of the AI in patients.

Additional Meeting Question Discussion:

Samsung question: Samsung considers to evaluate similarity in efficacy using ACR20 response rate as the primary endpoint at Week 16 instead of at Week 24 in the proposed Phase 3 study. Does the Agency agree that this approach is acceptable?

Samsung presented a justification for evaluating ACR20 response rate at Week 16 instead of Week 24. The Agency stated that evaluation of response at an earlier time point appeared reasonable.

3.0

PREA PEDIATRIC STUDY PLAN

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21U.S.C. 355c)], all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain 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(n) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. We encourage you to submit plans for pediatric studies during the IND stage of drug development.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were required.

6.0 ATTACHMENTS AND HANDOUTS

Attached are the slides presented by Samsung at the July 3, 2013 meeting between the FDA and Samsung.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA K LEE
08/01/2013